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ORIGINAL ARTICLE

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Switch from cyclosporine A to mycophenolate mofetil in nephrotic children

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Abstract Nephrotoxicity is a well-known adverse effect of cyclosporine A (CyA) treatment in children with steroid-dependent (SD) and steroid-resistant (SR) nephrotic syndrome (NS). We analyzed nine children (age: 3.3–15.7 years, two girls) with SD or SR NS who experienced a significant decrease in their GFR under CyA treatment as measured by inulin clearance (C_{IN}). Mycophenolate mofetil (MMF) was introduced progressively until doses of 1 g/1.73 m^2 twice daily were reached. CyA treatment was stopped after introduction of MMF and oral steroids were reduced if possible. After a median follow up of 261 days, no adverse effects of MMF such as diarrhea or hematological anomalies occurred in our patients. After switching from CyA to MMF, those children with SD NS remained in remission without proteinuria and those with SR NS did not show any significant changes in their residual proteinuria. The serum protein level did not change significantly in any of the children analyzed. GFR increased from a mean of 76.9±4.8 to 119.9±5.9 mL/1.73 m^2 per min (P<0.001). Oral steroid treatment could be reduced from a median [range] prednisone dose of 0.85 [0.26–2.94] mg/kg/d pre-MMF to 0.29 [0–1.1] mg/kg per day (P=0.026), and blood pressure decreased moderately after CyA withdrawal, but the difference did not reach statistical significance. We conclude that a switch from CyA to MMF seems to be safe for children with SDNS and SRNS in terms of side effects as well as disease control, at least in the short term. Interruption of CyA treatment lead to rapid amelioration of kidney function in these children, often associated with steroid sparing, which may lead to additional benefit for growth velocity, blood pressure and physical appearance.

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Introduction

A small proportion of children with initially steroid-responsive nephrotic syndrome (NS) run a multiply-relapsing or steroid-dependent course despite treatment with cyclophosphamide [1]. Some go into remission with cyclosporine A (CyA) but are dependent on this drug, which with prolonged exposure can lead to a decrease of renal function due to nephrotoxicity [2]. Indeed, chronic CyA nephrotoxicity leads to tubulointerstitial fibrosis causing progressive renal failure [2]. Reducing the dose of CyA in order to avoid further degradation of renal function increases the risk of disease relapse. Potential benefits and risks of long term CyA treatment are comparable for children with steroid-resistant and a steroid-dependent NS.

Mycophenolate mofetil (MMF) is an immunosuppressant drug which has an established role in solid organ transplantation; it inhibits inosine monophosphate dehydrogenase and thus de novo purine synthesis [3]. We investigated whether MMF was beneficial in terms of reduction of nephrotoxicity and disease control in patients with CyA-dependent NS.

Patients and methods

During the inclusion period, 73 inulin clearances (C_{IN}) were performed in 24 children with SDNS or secondary SRNS under oral CyA treatment. The mean (range) follow up period before switch to MMF was 12 (7–19) months. We report data from those patients with SDNS and SRNS, treated with CyA, who experienced a decrease in their glomerular filtration rate (GFR) as measured by C_{IN}. CyA trough levels were measured every 2–4 weeks. Nine children (age : 3.3–15.7 years, two girls, seven boys) were analyzed. C_{IN} was investigated every 3–6 months. As soon as C_{IN} was <100 ml/min per 1.73 m^2, MMF was initiated at 0.5–0.75 g per 1.73 m^2 and advanced as appropriate to 1.0 g per 1.73 m^2 twice daily. The

Table 1 Patient characteristics

Patient	Age (years)	Gender	Inulin clearance (ml/min per 1.73m^2)		Prednisone (mg/kg per day)		Proteinuria (g/day per 1.73 m^2)		Systolic blood pressure (mmHg)		BMI (kg/m^2)
			CyA	MMF	CyA	MMF	CyA	MMF	CyA	MMF	
1	13.75	F	82	107	0.67	0.23	0.0	0.0	121	128	22.5
2	7.9	M	87	120	0.41	0.42	3.0	0.0	113	88	30.1
3	3.25	M	74	106	2.94	1.1	5	0.0	115	90	23.2
4	15.67	F	76	101	1	0.13	0.0	0.0	117	106	26.2
5	9.75	M	52	120	0.63	0.31	3.0	3.0	117	110	17.6
6	14	M	79	101	0.37	0.09	0.0	0.0	126	121	29.7
7	4	M	94	116	0.26	0	0.3	0.0	112	100	15.2
8	14.75	M	91	122	1	0.25	5.1	1.3	114	105	15.3.
9	15.67	M	57	126	0.4	0.1	0.0	0.3	127	122	23.0

Age is given in decimal numbers; M=boy; F=girl; blood pressure, prednisone, proteinuria and weight are given under CyA before MMF introduction and at the end of the observation period under MMF. Patients 3 and 5 were secondary steroid-resistant. Blood pressure is given as a mean of three consecutive electronic measurements during the consultations

median (range) follow-up after switch to MMF was 261 (85–650) days. Plasma levels of mycophenolic acid (MPA)—the main metabolite of MMF—were evaluated weekly during the first month, then once per month, and were in the therapeutic range. Blood pressure was measured three times on each follow-up consultation. No gastrointestinal side effects nor hematological alterations, such as leukopenia, infections (apart from common cold disease), elevated hepatic enzymes, or elevated lipid levels were found in our patients. CyA was tapered off rapidly over two weeks. The patients received variable doses of steroids concomitant with initiation of MMF therapy, ranging from a low (0.5 mg/kg every other day) to a high daily dose prednisone of 2 mg/kg per day (Table 1). An effort was made to progressively reduce and, if possible, discontinue the steroid treatment. GFR was evaluated by inulin clearance 3–5 months after the switch to MMF.

Clinical details for the analyzed patients are summarized in Table 1. All patients were initially steroid responsive and turned out to be steroid-dependent after multiple relapses; two patients developed secondary steroid resistance. After introduction of CyA, residual proteinuria persisted in both steroid-resistant patients (Table 1).

Statistical analysis

The Kolmogorow-Smirnov test was used to analyze for normal distributions. Data were summarized as mean±standard error (SEM) for normally distributed data and as median and range for non-normally distributed data. Results were analyzed using a two-sample *t*-test, assuming unequal variances, to compare means. The level of statistical significance was set at $P<0.05$.

Results

Mean CyA trough levels over three months were in the therapeutic range for all analyzed children (96.2±6.59 ng/ml; mean±SE) and did not differ significantly ($p=0.28$) from those patients with no alteration in GFR (92.1±3.71 ng/ml). However the time on CyA was significantly longer in the group with reduced GFR (11.4±1.2 vs 7.3±1.0 months; mean±SE; $p=0,023$).

After the switch from CyA to MMF, those children with SDNS remained in complete remission, and the two patients with secondary SRNS presented a decrease in their residual proteinuria over the follow-up period of 261 (85–650) days (Table 1). Serum protein levels did not change significantly for any of the analyzed children. GFR, as measured by C_{IN}, increased significantly from (mean±SE) 76.9±4.8 to 119.9±5.9 ml/1.73 m^2 per min ($P<0.001$) (Fig. 1).

No adverse effects of MMF such as diarrhea or hematological anomalies occurred in our patients. White blood cell count did not differ significantly before and after MMF. Oral steroid treatment could be reduced from a median [range] prednisone dose of 0.85 [0.26–2.94] mg/kg/day pre-MMF to 0.29 [0–1.1] mg/kg per day ($P=0.026$), and blood pressure decreased moderately after CyA withdrawal, but the difference did not reach statistical significance (Fig. 1, Table 1).

Remission was maintained in all patients with SDNS over the follow-up period. Furthermore, the CyA-induced hypertrichosis, and moderate gingival hypertrophy disappeared in all children. No opportunistic infection occurred over the follow-up period.

Discussion

It is well-known that some patients under CyA treatment develop chronic renal failure due to CyA nephrotoxicity. While CyA-induced acute nephrotoxicity (vasoconstriction) is reversible, chronic nephrotoxicity (tubulointerstitial fibrosis and prolonged vasoconstriction) is, at least to a certain degree, irreversible. One strategy used to avoid CyA nephrotoxicity is dose reduction, which increases the risk of disease relapse and may necessitate an increase of steroid dosage, leading to the well-known side effects.

It is assumed that MMF is effective in the treatment of steroid-responsive patients [4, 5] due to a combination of its immunosuppressive properties and its other mechanisms of action. MPA, the pharmacologically active metabolite of MMF, inhibits both T and B lymphocyte proliferation, B lymphocyte antibody production, as well as the glycosylation and expression of adhesion molecules [3, 6, 7, 8, 9, 10]. In addition, MPA has been shown to inhibit vascular smooth muscle cell [8] and mesangial cell

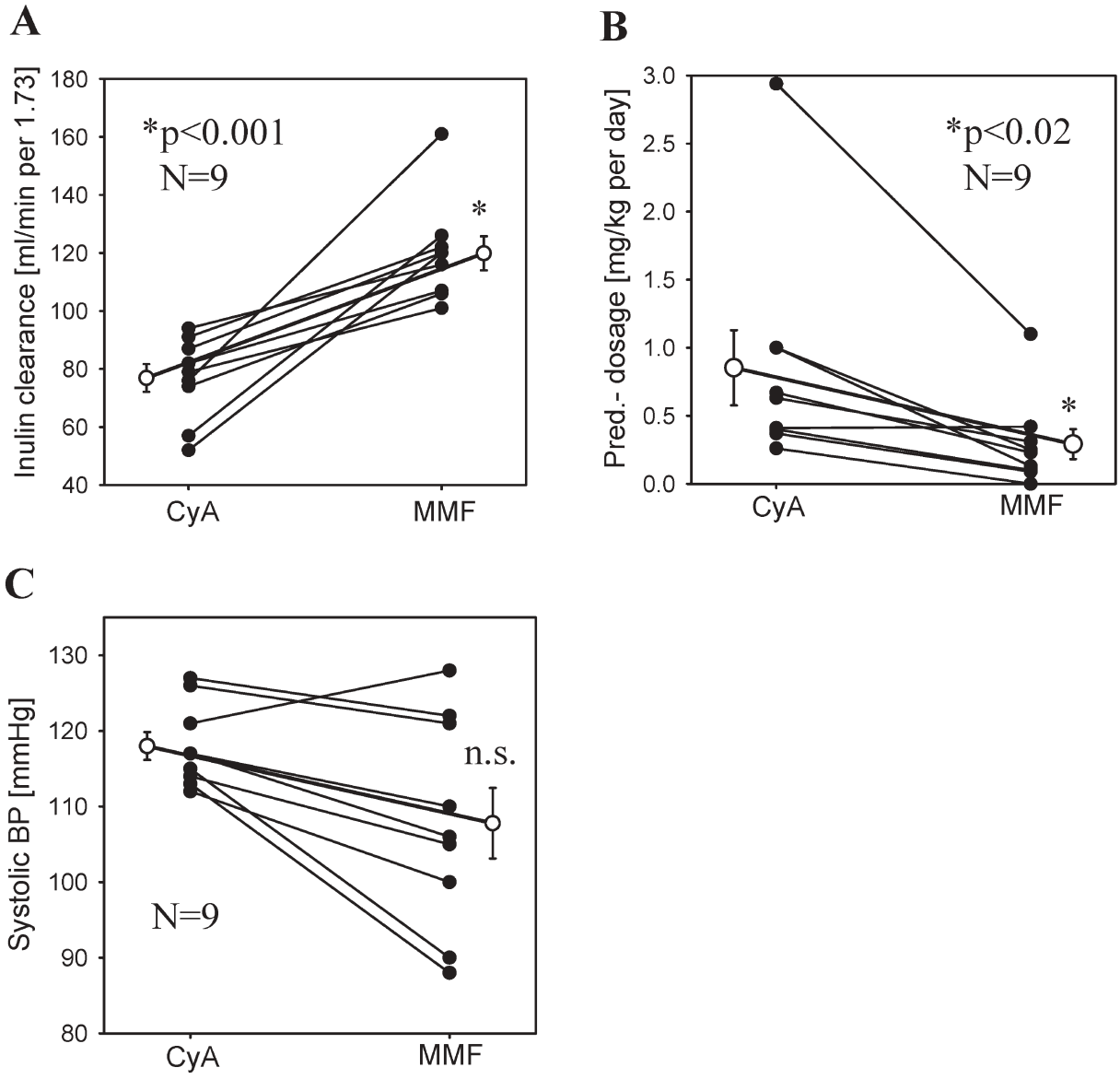

Fig. 1 Inulin clearance (**A**), prednisone dosage (**B**) and systolic blood pressure (**C**) under CyA and after switch to MMF. *Open circles* mean±SEM; *closed circles* patient 1–9

proliferation [11], to be a selective inhibitor of inducible nitric oxide synthase [12], and to induce apoptosis in activated T cells [13]. One or a combination of these actions could account for the observed amelioration of various experimental models of glomerular disease, including active [14] and passive Heymann nephritis, hyperfiltration injury in the remnant kidney [15], mesangial proliferative nephritis [11], and murine lupus nephritis [16]. These same mechanisms are likely to be able to control the inflammation and/or structural remodeling characteristic of human glomerular diseases.

Historically, the treatment of multiply-relapsing or steroid-resistant patients has included either CyA or a cytotoxic drug. Unfortunately, steroid resistance also often predicts resistance to these second line immunosuppressive drugs. In addition, CyA dependency has often been the trade-off for steroid dependency, and cytotoxic drugs have their own toxicities. The potential role for MMF in steroid±CyA-dependent NS is that of an effective steroid-sparing agent without the potential adverse renal, hemodynamic, metabolic, and cosmetic effects of CyA [17]. Similar to the situation with CyA, a proportion of responsive patients will be found to be MMF-dependent and relapse when treatment is discontinued. Whether a long term MMF treatment is more beneficial for patients than a long term CyA treatment in terms of adverse effects and disease control has to be evaluated in larger, controlled studies.

The kidney function of our patients has been evaluated by C_{IN} measurements twice a year. As soon as the GFR

decreased to below 100 ml/min per 1.73 m^2, the children were switched to MMF and CyA was rapidly tapered off over two weeks. The patients' kidney function improved rapidly, suggesting an at least partial reversibility of CyA toxicity after long term treatment. Morphological changes do not seem to play a major role in renal impairment in these settings. In order to detect renal impairment rapidly and avoid morphological alteration we perform inulin clearances regularly. It is known that the disease activity of the NS may decrease over several years. It can therefore be hypothesized that after an initial benefit (rapid disease control), the benefit risk ratio changes later on in the clinical course under prolonged CyA treatment, suggesting a beneficial role of MMF in this setting.

In conclusion, the switch from CyA to MMF in SDNS allows a significant recovery of the GFR in addition to a possible steroid-sparing effect, at least in the short term. Such a strategy may therefore lead to additional benefits, such as growth velocity, physical appearance, and blood pressure control.

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