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Long-term beneficial effects of azathioprine addition to ongoing cyclosporine-prednisone protocol in renal transplantation

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Abstract. Delayed addition of azathioprine (Aza) to an ongoing cyclosporine-prednisone protocol was started 11.3 ± 9.9 months after renal transplantation in 31 patients. Group I ($n = 10$) had chronic renal function deterioration due to chronic rejection, group II ($n = 11$) had repeated or severe acute rejection episodes and group III ($n = 10$) had cyclosporine (Cs) toxicity despite drug tapering. In group I, SCr had risen over the 6 months prior to Aza addition ($P < 0.05$), renal function declining at a rate of -0.13 ± 0.12 SCr^{-1}. In the 6 months post-Aza, renal function improved at a rate of 0.05 ± 0.07 SCr^{-1}, and during the entire follow-up at a rate of 0.05 ± 0.12 SCr^{-1} ($P < 0.01$) with stable Cs levels. In group II the decline in renal function was greater, though the rate of decline was stopped after Aza. In group III, renal function improved in eight patients. After 23 ± 12 months of follow-up, 15 patients had improved graft function, two were stable, 12 had worsened (nine on dialysis) and two had died. Amelioration of chronic graft dysfunction can be achieved by delayed addition of Aza to Cs-prednisone-treated renal allograft patients with chronic rejection or Cs toxicity, with long-term beneficial effects in a high proportion of patients.

Key words: Renal transplantation – Cyclosporine – Azathioprine – Triple therapy – Chronic rejection

The best approach to management of chronic renal allograft dysfunction in cyclosporine (Cs) treated renal transplant (RT) patients has not yet been defined. The current study describes short- and long-term benefits of adding azathioprine (Aza) to Cs-treated RT patients with chronic graft dysfunction due to chronic rejection, repeated or severe acute rejection episodes or Cs toxicity.

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Methods

Between March 1986 and March 1991, 200 non-diabetic patients received a cadaveric renal allograft at our hospital. Immunosuppression consisted of Cs (5 mg/kg per day) i. v. for 2 days and then oral Cs (10–12 mg/kg per day) adjusted to give total blood levels (TDx, Abbott, Chicago) in the range 400–800 ng/ml for 1 month and 200–400 ng/ml thereafter. Prednisone was given at a dose of 0.5 mg/kg per day for 1 week and then tapered to 10 mg/day after 1 month. Aza (1–2 mg/kg per day) was added 11.3 ± 9.9 months after RT for 31 of the

Table 1. Renal function and Cs levels before and after addition of Aza to an ongoing Cs-prednisone

	6 months	Aza	6 months	Last visit
Group I				
Number of patients	10	10	10	7
SCr[a]	193 ± 25	255 ± 19	228 ± 22	220 ± 33
1/SCr[b]	0.50 ± 0.05	0.36 ± 0.03	0.41 ± 0.04	0.31 ± 0.08
Cs levels[c]	436 ± 52	286 ± 53	236 ± 54	184 ± 21
Group II				
Number of patients	3	11	8	4
SCr	194 ± 30	290 ± 18	299 ± 43	211 ± 35
1/SCr	0.46 ± 0.07	0.37 ± 0.06	0.23 ± 0.17	0.21 ± 0.08
Cs levels	266 ± 49	332 ± 123	275 ± 33	250 ± 44
Group III				
Number of patients	6	10	10	9
SCr	166 ± 18	210 ± 19	165 ± 14	167 ± 17
1/SCr	0.57 ± 0.08	0.45 ± 0.04	0.57 ± 0.07	0.52 ± 0.09
Cs levels	741 ± 182	469 ± 34	277 ± 40	318 ± 67
All patients				
Number of patients	19	31	28	20
SCr	189 ± 14	253 ± 11	228 ± 18	198 ± 15
1/SCr	0.51 ± 0.04	0.39 ± 0.02	0.40 ± 0.04	0.35 ± 0.05
Cs levels	506 ± 72	361 ± 26	262 ± 25	257 ± 34

Data are mean ± SEM
[a] serum creatinine (μmol/l), excluding graft loss
[b] including 1/SCr = 0 for graft loss (SCr in mg/dl)
[c] in ng/ml
See text for statistical significance

Table 2. Evolution of renal function before and after Aza addition evaluated by the rate of change in 1/SCr

Group	6 months before Aza		Aza start vs. 6 months later	Aza start vs. last follow-up
I	–0.13 ± 0.03	Only functioning grafts	0.05 ± 0.02	0.05 ± 0.02
		1/SCr = 0 for graft loss	0.05 ± 0.02	–0.05 ± 0.06
II	–0.15 ± 0.05	Only functioning grafts	0.04 ± 0.05	0.19 ± 0.07
		1/SCr = 0 for graft loss	–0.03 ± 0.06	–0.11 ± 0.08
III	–0.07 ± 0.04	Only functioning grafts	0.13 ± 0.04	0.13 ± 0.05
		1/SCr = 0 for graft loss	0.13 ± 0.04	0.13 ± 0.05
All	–0.11 ± 0.03	Only functioning grafts	0.08 ± 0.02	0.11 ± 0.03
		1/SCr = 0 for graft loss	0.05 ± 0.03	–0.01 ± 0.04

See text for numbers of grafts in each group and situation and statistical significance

Table 3. Outcome of patient survival and graft function after addition of Aza

	Group (n)			
	I (10)	II (11)	III (10)	All (31)
At 6 months				
Better	7	3	8	18
No change	1	1	1	3
Worse	2	4	1	7
Lost (dialysis)	0	1	0	2
Dead	0	1	0	1
At last follow-up				
Months after Aza	24.9 ± 3.8	16.8 ± 3.8	28.3 ± 2.8	23.1 ± 2.1
Better	3	4	8	15
No change	2	0	0	2
Worse	2	0	1	3
Lost (dialysis)	3	6	0	9
Dead	0	1	1	2

patients. Group I ($n = 10$) had chronic renal allograft dysfunction due to chronic rejection (80% biopsy proven), group II ($n = 11$) had repeated or severe acute renal allograft rejection unresponsive to methylprednisolone boluses, and group III ($n = 10$) had Cs toxicity despite adequate blood levels and drug tapering. The time to initiation of Aza was 19.6 ± 2.8, 5.9 ± 1.8 and 8.9 ± 3 months, respectively. Data are expressed as mean ± SEM and Student's t-test was used for the statistical analysis.

Results

Renal function and Cs levels before and after addition of Aza, rates of renal function changes and outcome of grafts and patients are given in Tables 1–3.

Group I. Three patients lost their grafts 15, 19 and 20 months after Aza addition. Serum creatinine (SCr) had risen over the 6 months prior to Aza addition ($P < 0.05$), renal function declining at a rate of –0.13 ± 0.03 SCr^{-1}. In the 6 months post-Aza renal function improved at a rate of 0.05 ± 0.02 SCr^{-1} ($P < 0.001$) and during the entire follow-up at a rate of 0.05 ± 0.02 SCr^{-1} excluding the three patients with graft loss ($P < 0.01$). Cs levels did not change significantly.

Group II. Renal function declined at a rate of –0.15 ± 0.05 SCr^{-1} before Aza was stopped 6 months after starting (0.04 ± 0.05, $n = 8$, $P < 0.025$), when one patient had died of pneumonia and another two had lost their grafts at 4 months. Graft loss also occurred in four patients after 10–19 months after Aza addition. Four patients had improved graft function (rate 0.19 ± 0.07 SCr^{-1}) 28.2 ± 6.5 months after Aza. Cs levels were stable.

Group III. Renal function improved 6 months after Aza addition (–0.07 ± 0.04 vs. 0.13 ± 0.04 SCr^{-1}, $P < 0.01$) and this good function was still stable at the last follow-up. One patient died of myocardial infarction 34 months after RT. Only one patient had worse graft function after Aza addition. Cs levels were able to be significantly decreased ($P < 0.005$, basal vs. 6 months; $P < 0.01$, basal vs. last follow-up).

The rate of renal function deterioration for the whole series before Aza addition (–0.11 ± 0.03 SCr^{-1}) had been reversed 6 months after Aza (0.08 ± 0.02 SCr^{-1}, $n = 28$, $P < 0.001$) and at the last follow-up (0.11 ± 0.03 SCr^{-1}, $n = 21$, $P < 0.001$). Considering $SCr^{-1} = 0$ in cases of graft loss, the rates are 0.05 ± 0.03 SCr^{-1} ($n = 31$, $P < 0.001$) at 6 months and –0.01 ± 0.04 SCr^{-1} ($n = 31$, $P < 0.05$) at the end of follow-up. Considering the whole series, Cs levels were decreased after Aza addition ($P < 0.02$).

Discussion

Controlled or routine conversion from Cs to Aza after RT has been attempted to avoid Cs toxicity [3, 4]. However, high rates of acute rejection have been reported [4]. Perioperative triple-drug therapy has given better rejection control, but at the expense of more serious infections and even neoplasms [1] and with unclear advantages regarding patient and graft survival. Our approach of delaying the addition of Aza to an ongoing Cs-prednisone protocol has been of clear benefit for a substantial proportion of patients with dysfunction due to chronic rejection. The reversal in the rate of change in renal function from negative to positive is highly significant in this group, with 70% of functioning grafts after a mean of 2 years of follow-up.

Other groups have reported similar benefits, but with a shorter follow-up [2, 5].

Although advantages of Aza addition in patients with repeated or severe acute rejection episodes are less clear, 36% had functioning grafts after a mean of 16.8 months of follow-up, a significant proportion if we consider that Aza was really rescue therapy in this group.

Aza addition in patients with Cs toxicity despite normal drug levels allowed a decrease in Cs doses and levels without compromising immunosuppression. After a mean of 28 months, eight out of ten patients had improved renal function and another one had died with a functioning graft: reversal of the rate of graft function deterioration was very evident.

Amelioration of chronic graft dysfunction can be achieved by delayed addition of Aza to Cs-prednisone-treated RT recipients with chronic rejection or Cs toxicity, with long-term beneficial effects in a high proportion.

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