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CSA/AZA, in the absence of prednisone, improves linear growth in renal transplanted children

E. David-Neto, W. Nahas, E. C. Sampaio, L. E. Ianhez, E. Sabbaga, and S. Arap

Unidade de Transplante Renal, Servico de Urologia, Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Brazil

Abstract. We compared the results of 44 renal transplants in children, of whom 24 were treated with CSA/AZA and 20 with prednisone in combination with AZA and/or CSA. There were no differences in age distribution or mean ages at transplant between the two treatment groups. The CSA/AZA group had a longer follow-up (29 ± 33 vs 17 ± 18 months). At the last follow-up, five children in the CSA/AZA and none in the prednisone group had lost their grafts. Serum creatinine increased in both groups from 0.7 ± 0.1 mg/dl and 0.9 ± 0.1 mg/dl at the end of the first month to 1.1 ± 0.2 mg/dl in the 36th month (CSA/AZA group) ($P < 0.0001$) and to 1.5 ± 0.6 mg/dl in the 18th month (prednisone group) ($P < 0.05$), respectively. Total cholesterol level was 189 ± 52 mg/dl and 178 ± 60 mg/dl and LDL level was 117 ± 48 mg/dl and 115 ± 51 mg/dl for the prednisone and CSA/AZA groups, respectively. HDL was greater in the CSA/AZA group (50 ± 10 vs 41 ± 10 mg/dl) ($P < 0.03$), and VLDL was greater in the prednisone group (31 ± 13 vs 22 ± 8 mg/dl) ($P < 0.05$). Serum triglyceride was greater in the prednisone group (174 ± 93 vs 112 ± 50 mg/dl) ($P < 0.03$). The standard deviation score for height of the children in the prednisone group did not change (−2.4 ± 1.4 vs −2.1 ± 1.4 SDS), whereas the SDS height score for the CSA/AZA children increased from −3.1 ± 1.7 to −2.6 ± 1.5, −1.9 ± 1.4 and −1.7 ± 1.4, at 12, 24 and 36 months, respectively ($P < 0.001$). CSA/AZA is a good immunosuppressive regime for the first renal transplant in children, but only 75% tolerated AZA/CSA without same damage to their grafts.

Key words: Renal transplantation – Pediatric – Growth – Cyclosporin A – Prednisone

Steroids used for chronic immunosuppression in renal transplantation (RTx) inhibit linear growth in paediatric recipients. Since December 1986 we have performed RTx in children followed by triple therapy (CSA/AZA/PRED), stopping the prednisone (PRED) after 6 months in order to improve linear growth. The results of this treatment regime are described here.

Offprint requests to: Dr. E. David-Neto, R. Ferdinando Laboriau, 263, CEP: 01250, Sao Paulo-Brazil

Material and methods

A total of 44 children weren enrolled in this study, 24 of them in the CSA/AZA group and 20 in the PRED group, associated with either AZA or CSA or both. The CSA/AZA group comprised 12 children on triple therapy who had PRED withdrawn at 6 months after RTx and 12 who were transplanted a few years before the study started. These children had been maintained on AZA/PRED which was switched to CSA/AZA.

The PRED group comprised children who for various reasons could not have PRED removed from their immunosuppressive regime. The reasons for not stopping PRED were: retransplants (5), CSA nephrotoxicity (2), adequate growth while on PRED (2), nephrotic syndrome (1), haemolytic-uraemic syndrome (1), chronic hepatic disease (1), urinary disorder (1), frequent rejection (2) and parental decision (2). Of these 20 children, four were on AZA/PRED, one on CSA/PRED and 15 on CSA/AZA/PRED.

PRED was started in both groups at 1 mg/kg per day and progressively tapered to 0.12–0.15 mg/kg per day (PRED group) or completely withdrawn by 6 months (CSA/AZA group). CSA was started at 10 mg/kg per day. The dosage was then adjusted to keep the whole-blood trough level (RIA monoclonal specific) around 100–150 ng/ml. AZA was started and kept at 2 mg/kg per day whenever possible.

Table 1. Ages at the start of the study

Age (years)	PRED group	AZA/CSA	Significance of difference
1– 6	6	2	NS
6–12	7	12	NS
12–16	3	7	NS
> 16	4	3	NS
Mean + SD	10 ± 5 years	11 ± 4 years	NS
Follow-up (months)			
Mean ± SEM	17 ± 18	29 ± 33	
Range	3–52	3–55	

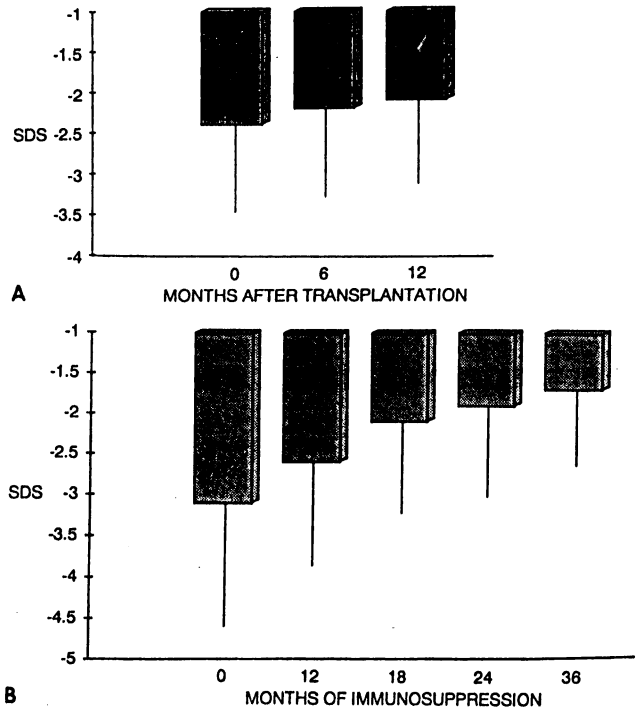

Fig. 1 a, b. Change in standard deviation scores for height after transplantation. **a** PRED group ($P < 0.118$); **b** CSA/AZA group ($P = 0.000$)

The children in both groups had the same age distribution, as seen in Table 1. Mean follow-up was longer in the CSA/AZA than in the PRED group. For this reason we compared data between both groups up to the 18th month.

All results are expressed as mean ± SEM. For continuous variables, analysis of variance was used. Analysis of data between groups was done using, the two-tailed *t*-test for independent samples with the help of the STATS software.

Results

Serum creatinine (SCr) increased slightly but steadily in both groups. It increased from 0.7 ± 0.1 mg/dl and 0.9 ± 0.1 mg/dl at the end of the first month to 1.1 ± 0.2 mg/dl in the 36th month ($P < 0.0001$) and 1.5 ± 0.6 mg/dl in the 18th month ($P < 0.05$) for the CSA/AZA and PRED group, respectively. There was no difference between the SCr curves up to the 18th month.

In the CSA/AZA group, at the final follow-up, three children had to switch to AZA/PRED because of CSA nephrotoxicity. Two of them are currently well with a mean SCr of 1.2 ± 0.2 mg/dl. The third child lost her graft 1 year later. Four other children in this group lost their grafts, one because of non-compliance, one because of a mistreat acute rejection, one because of haemolytic-uraemic syndrome and one because of arterial thrombosis attributed to CSA toxicity. None of the children in the PRED group lost their graft.

There was no difference in the total and LDL cholesterol levels between the groups. Total cholesterol level was 189 ± 52 mg/dl and 178 ± 60 mg/dl and LDL level was 117 ± 48 and 115 ± 51 mg/dl for the PRED and CSA/AZA groups, respectively. On the other hand, HDL in the CSA/AZA was greater than in the PRED group (50 ± 10 vs 41 ± 10 mg/dl) ($P < 0.03$), and VLDL was greater in the PRED group than in the CSA/AZA group (31 ± 13 vs 22 ± 8 mg/dl) ($P < 0.05$). Serum triglyceride was greater in the PRED group than in the CSA/AZA group (174 ± 93 vs 112 ± 50 mg/dl) ($P < 0.03$).

AT RTx the children in the PRED group were −2.4 ± 1.4 standard deviation score (SDS) for height. One year later the score had not changed significantly (−2.1 ± 1.4 SDS). In contrast, in the CSA/AZA group, SDS increased from −3.1 ± 1.7 to −2.6 ± 1.5, −1.9 ± 1.4 and −1.7 ± 1.4, at 12, 24 and 36 months ($P < 0.001$).

Discussion

This study illustrates that PRED added to the immunosuppressive regimes for children undergoing RTx leads to some adverse effects that deserve a review of its real need in such recipients, at least on first RTx and in low-risk cases.

We were able to discontinue PRED in 75 % of our first RTx paediatric recipients. In the remaining 25 %, there was either a rejection episode or CSA nephrotoxicity that forced us to reintroduce PRED. These children are currently being treated with another kind of steroid supposed not to have the same adverse effects on growth.

In our group of children, we observed five graft losses in the CSA/AZA group and none in the PRED group. However, all graft losses occurred after a mean of 15 months of CSA/AZA treatment (16 ± 8 months), except for one which occurred in the fourth month (mistreat rejection). As the mean follow-up of the PRED group was currently only 17 months, it is possible that the difference between the two groups in terms of graft loss may disappear with a longer follow-up.

In both groups we observed a steady deterioration of renal function. It was not clear whether this was due to CSA nephrotoxicity or chronic ongoing rejection.

The CSA/AZA group had lower levels of triglyceride and VLDL and higher levels of HDL. Serum lipids have been reported to be higher in patients on CSA/PRED than in patients on AZA/PRED [2]. In our PRED group, 80 % of the patients were also on CSA, and this combination of drugs proved to be more deleterious to serum lipids than the CSA/AZA combination. This raises the possibility that the threat of hyperlipidaemia is not from the CSA, but from the steroids associated with CSA in most protocols. On the other hand, we should note that, al-

Table 2. Linear growth of children in the AZA/CSA group

SDS	Number of children in each category		Significance of difference
	Start	Last follow-up	
−1 – 0	0	7	$P < 0.002$
−1 – −2	7	5	NS
−2.1 – −3	9	3	NS
< −3	8	3	NS
Total	24	18	

SDS, standard deviation score

though higher than in CSA/AZA group, the serum lipids in the PRED group remained within the normal range.

The most striking difference between the two groups was seen in linear growth. We have already demonstrated that PRED in high doses blocks nocturnal GH secretion and in lower doses blocks somatomedin-C activity [3]. In our PRED group the use of 0.12–0.15 mg/kg per day impaired growth. One year after RTx, the children remained −2 SDS below the mean for the height they had been at the time of RTx (Fig. 1a) and probably will attain adulthood still −2 SDS below mean height, as extensively demonstrated in the literature.

In contrast, the CSA/AZA group demonstrated a catch-up growth of +0.6 SDS per year (Fig. 1b). At the final follow-up, seven of the CSA/AZA children were less than 1 SDS below the mean height for their age (Table 2). If the +0.6 SDS per year catch-up growth continues in the years to come we except that all children will be of normal height.

In summary, CSA/AZA was shown to be an excellent immunosuppressive regime for first RTx in paediatric recipients. However, only 75% of the children tolerated such a regime. The other 25% still await a new approach which will allow an improvement in their linear growth.

The use of human recombinant GH in very high doses has not been tried by us because the published results on this subject demonstrate an increase in growth rate but do not show a true catch-up growth as evidenced by either the maintenance or a decrease in the SDS for height [1].

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