Transpl Int (1998) 11 [Suppl 1]: S328–S330

C. Peter
K. Latta
D. Graf
G. Offner
J. Brodehl

Does tacrolimus cause more severe anemia than cyclosporine A in children after renal transplantation?

C. Peter · K. Latta (✉) · D. Graf · G. Offner · J. Brodehl
Kinderklinik MHH, Department of Pediatric Nephrology, 30623 Hannover, Germany
Tel. +49-511-532 3220; Fax +49-511-532 3911

Abstract Initial reports indicated the possibility of severe anemia associated with tacrolimus (TC) therapy. We investigated the degree of anemia under TC treatment in comparison to cyclosporine A (CsA) treatment in children after renal transplantation. A cross-sectional analysis of 95 children successfully transplanted for at least 3 months was performed. Eighty-five children received CsA and 10 TC. TC-treated patients were compared with CsA-treated patients who were matched according to age, gender, creatinine clearance, and time after transplantation. No patient received additional therapy with mycophenolate mofetil or azathioprine. The creatinine clearance of the whole group of transplanted children was 58 ml/min per 1.73 m^2. The patients within the matched-pair analysis had a lower creatinine clearance (TC 46 and CsA 48 ml/min per 1.73 m^2). The hemoglobin was 10.3 g/dl for the TC-treated children and 10.4 g/dl among the CsA-treated patients. Numerically, EPO was higher and iron lower in the TC group than in the CsA group. Among children with functioning renal grafts, a correlation exists between Hb and creatinine clearance. A significant difference in the degree of anemia between TC- and CsA-treated children could not be found.

Key words Tacrolimus · Cyclosporine A · Renal transplantation · Anemia · Children

Introduction

Tacrolimus (TC) is a potent immunsuppressive agent which has been used after solid organ transplantation. The main indication for its use after kidney transplantation is steroid-resistant rejection, where TC can successfully be used without monoclonal antibodies. A variety of side effects has been described among which nephro- and neurotoxicity are the most frequent and important ones [2, 4]. Furthermore, severe anemia was reported in a single case as well as in a series of pediatric patients after heart transplantation [2, 5]. In the latter study, 8 out of 49 children developed severe anemia (Hb < 8 g/dl). Thus, we examined whether children after kidney transplantation develop a more severe anemia under TC therapy than under cyclosporine A (CsA) therapy.

Patients and methods

In a prospective, cross-sectional analysis were evaluated hematological parameters in 95 children after kidney transplantation. All children were successfully transplanted for at least 3 months. Eighty-five patients received CsA, and 10 patients TC as immunosuppressant. The indication for TC therapy was steroid-resistant rejection in 8 out of 10 children. The mean age was 14.4 ± 4.7 years. Thirty-three had received a living related graft and 62 a cadaveric graft. While the mean time after transplantation was 4.7 ± 3.2 years in the CsA patients, this interval amounted to 2.3 ± 1.3 in the TC patients. The average creatinine clearance was 58 ± 23 ml/min per 1.73 m^2 (CsA) and 46 ± 18 ml/min per 1.73 m^2 (TC), respectively. The following parameters were measured during routine examination (no child underwent an additional venipuncture). Besides serum creatinine, blood concentrations of immunosuppressant, hemoglobin concentration, and standard hematological indices (erythrocyte count, MCHC, MCV, and platelets),

Table 1 Hematological parameters of 10 tacrolimus (TC)-treated patients and 85 cyclosporine A (CsA)-treated patients. Values are means ± SD

	TC-treated patients	CsA-treated patients
Hemoglobin (g/dl)	10.3 ± 1.6	11.1 ± 1.6
Erythrocytes ($\times 10^6/\mu l$)	3.8 ± 0.7	3.9 ± 0.6
MCV (fl)	79.5 ± 5.4	84.4 ± 5.3
MCHC (g/dl)	33.9 ± 0.9	34.1 ± 0.7
Thrombocytes ($\times 10^3/\mu l$)	258.0 ± 78.6	272.0 ± 74.8
Vitamin B12 (pmol/l)	457.0 ± 241.0	432.0 ± 237.0
Folic acid (nmol/l)	25.0 ± 8.7	21.7 ± 9.0
Erythropoietin (U/l)	19.5 ± 10.6	13.6 ± 6.5
Iron (μmol/l)	9.5 ± 4.0	13.3 ± 4.7
Iron-binding capacity (μmol/l)	61.3 ± 15.3	65.1 ± 11.2
Ferritin (μg/l)	17.0 ± 11.5	54.6 ± 139.7

erythropoietin, folic acid, vitamin B12, iron, iron-binding capacity, and ferritin were assessed. For a correct comparison of the two different groups, a matched-pair analysis was performed. Ten CsA-treated children were selected according to age, gender, and calculated creatinine clearance. Statistical comparison was done by a Wilcoxon test. Correlation was calculated with standard software (JMP for MacIntosh). A P value < 0.05 was considered significant.

Results

The hemoglobin values of all the transplanted children showed an approximate binominal distribution with a mean of 11.1 ± 1.6 g/dl. For the TC-treated children hemoglobin was slightly lower with a mean of 10.3 ± 1.6 g/dl (NS). Further serological and hematological parameters are shown in Table 1. A few patients with a high number of transfusions during dialysis had vastly elevated ferritin concentrations. Figure 1 depicts the correlation between creatinine clearance and hemoglobin concentration. The regression line was calculated to by $y = 0.035x + 9.07$ ($R2 = 0.24$). Thus, the hemoglobin concentration correlates with the creatinine clearance. The figure depicts, with different symbols, the two modes of immunosuppression. According to this scattergram, hemoglobin levels appear to be independent from the immunosuppression. To further test this hypothesis, a matched-pair analysis, as described above, was performed. Matching for creatinine clearance led to equal values in both groups. CsA-treated patients showed a clearance of 48 ml/min per 1.73 m^2, while TC-treated patients had a clearance of 46 ml/min per 1.73 m^2. The hemoglobin was 10.3 g/dl for the TC-treated patients and 10.4 g/dl among the CsA-treated patients. Thus, in the matched-pair analysis the degree of anemia was the same. At the same time, EPO concentrations were 12.4 U/l (TC) and 19.5 U/l (CsA), respectively. This difference

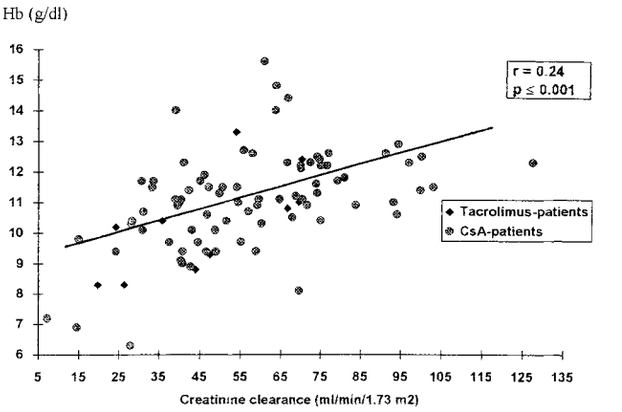

Fig. 1 Hemoglobin values (g/dl) in correlation with the creatinine clearance (ml/min per 1.73 m^2). Tacrolimus-treated patients marked as *diamonds* ($n = 10$), CsA-treated patients marked as *points* ($n = 85$)

did not reach statistical significance. The remaining parameters which were examined (Table 1) did not show numerical or statistical differences. Thus, after correction for creatinine clearance, no significant differences in erythropoeitin concentrations and the degree of anemia could be demonstrated between the TC- and CsA-treated groups.

Discussion

Various side effects have been observed under TC therapy. Anemia has infrequently and inconsistantly been reported [1–5]. Our prospective cross-sectional study examined the degree of anemia after pediatric kidney transplantation. A significant and positive correlation could be found for creatinine clearance and hemoglobin concentration. This was independent of the mode of immunosuppression. Patients treated with TC had a lower mean creatinine clearance (46 versus 58 ml/min per 1.73 m^2) than the whole group of patients. This can be explained by the most frequent indication for TC, which was steroid-resistant rejection (8 out of 10 children). Numerical differences, i.e., higher erythropoietin concentrations and lower iron levels among the TC-treated patients, were not statistically significant. In the matched-pair analysis, patients with comparable creatinine clearance (TC vs CsA: 46 versus 48 ml/min per 1.73 m^2) revealed no difference in their degree of anemia (TC versus CsA: Hb 10.3 and 10.4 g/dl).

References

1. Abu-Elmagd KM, Bronsther O, Kobayashi M, Yagihashi A, Iwaki Y, Fung J, Alessiani M, Bontempo F, Starzl T (1991) Acute hemolytic anemia in liver and bone marrow transplant patients under FK 506 therapy. Transplant Proc 23: 3190–3192
2. Asante-Korang A, Boyle GJ, Webber SA, Miller SA, Fricker FJ (1996) Experience of FK 506 immune suppression in pediatric heart transplantation: a study of long-term adverse effects. J Heart Lung Transplant 15: 415–422
3. Schneck FX, Jordan ML, Jensen CWB, Shapiro R, Tzakis A, Scantlebury VP, Ellis D, Gilboa N, Simmons R, Hakala TR, Starzl TE (1992) Pediatric renal transplantation under FK-506 immunosuppression. J Urol 147: 1585–1587
4. Shapiro R, Fung JJ, Jain AB, Parks P, Todo S, Starzl TE (1990) The side effects of FK 506 in humans. Transplant Proc 22: 35–36
5. Winkler M, Schulze F, Jost U, Ringe B, Pichlmayr R (1993) Anaemia associated with FK 506 immunosuppression. Lancet 341: 1035–1036