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Preventive OKT3 treatment with cyclosporine (Sandimmun) for second kidney transplantation

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Abstract A total of 793 kidney transplantations (KTx) were performed from November 1073 to March 1993. Two hundred and forty-two patients were treated with conventional immunosuppression (azathioprine + prednisolone) and all the others with cyclosporine (Sandimmun) and prednisolone (SIM + PRED). The survival of the second graft was less good in both therapeutic groups than that of the first ones, so we have started to use preventive immunotherapy with OKT3 (CILAG) in combination with SIM (both before operation) and PRED. We compared 32 SIM-PRED patients with 20 OKT3 + SIM + PRED patients. All underwent a second KTx. The two groups were found to be comparable and homogeneous with regard to 14 of 18 parameters analysed statistically. Statistically significant differences were found between the two groups as regards the frequency of acute rejection within 30 days (46.69% vs 20%), the delta creatinine value on the 1st and 2nd postoperative days (−4,3: −8 vs −8.6: −19.7%), patient survival after 4 years (78.2 vs 100%), and graft survival after 1 and 4 years (−58.9: −42.8 vs −83.5: −83.5%), with better results in the OKT3 group. We conclude that the preventive use of OKT3 simultaneously with SIM + PRED for the second KTx is the method of choice to prevent rejection and improve survival. This treatment results in patient and graft survival following the second KTx being as good as after the first KTx with SIM + PRED.

Key words Immunosuppression
Second kidney transplantation
OKT3 · Preventive treatment

Introduction

Cyclosporine (Sandimmun) has significantly improved survival of the first kidney transplantation as well as that of the second one [1, 2, 6, 12, 21]. However, the survival of the second grafts remains inferior to that of the primary ones, mainly due to the immunological reasons. Our aim was to use a stronger immunosuppressive regimen as preventive treatment in order to achieve better results. In the literature, studies have compared triple therapy azathioprine + Sandimmun + prednisolone and prevention with OKT3 as sequential therapy. There are very few publications about the use of cyclosporine simultaneously with OKT3, starting at the time of surgery [3, 8, 9, 12, 14, 21, 22, 24].

Patients and methods

Between November 1973 and March 1993 we performed 793 kidney transplantations, 721 of them with cadaveric kidneys while 72 were from living donors. These included 734 first, 57 second and 2 third grafts. The male/female ratio was 494/299. Mean age was 36.7 ± 7.2 years (including 42 children). Two hundred and forty-two patients were treated with conventional immunosuppression (AZA + PRED) and all the others with Sandimmun and prednisolone (SIM + PRED). Standard surgical procedures were used except for urinary tract reconstruction, which in most cases was the ureteroureterostomy. Thirty-two SIM + PRED patients were compared with 20 OKT3 + SIM + PRED patients. In both groups all drugs were started 2–4 h before surgery. In the SIM + PRED group 4 mg/kg per 24 h SIM was given IV by pump in the first 2 days and then continued with a dosage of 12 mg/kg per 24 h SIM by mouth divided into two daily doses and adjusted to the whole blood level of 200–400 ng measured by the TDX monoclonal method. A standard low dose of PRED was administered (0.5 mg/kg per day tapering at 2-week intervals). The immunosuppression in the OKT3 + SIM + PRED groups (5 mg/day OKT3) was given IV over 10 days with half a dose of SIM being given during the first 7 days and a full dose thereafter. If the SIM whole blood level did not reach the therapeutic level, OKT3 was continued. We evaluated the rate of acute tubular necrosis (ATN), early kidney function (creatinine clearance and delta creatinine in the first two 24-h periods), the rejection rate within 30 days following the operation and after the whole survival period, the number of first, second and third rejections and their rate of irreversibility, and the 1- and 4-year patient and graft survival rate.

Results

To compare the two groups we analysed 18 parameters. Fourteen of these (Table 1) did not differ, so the groups were homogeneous and comparable. We found a significant difference in the occurrence of ATN after transplantations. The difference between the early function of the pairs of kidneys transplanted as a first or second procedure suggested to us that the immunological processes played a more important role in the second transplantation than the donor factors. This fact confirmed our suspicions. The early functions evaluated by endogenous creatinine clearance and the decrease of serum creatinine (delta creatinine) and, of course, by urinary output

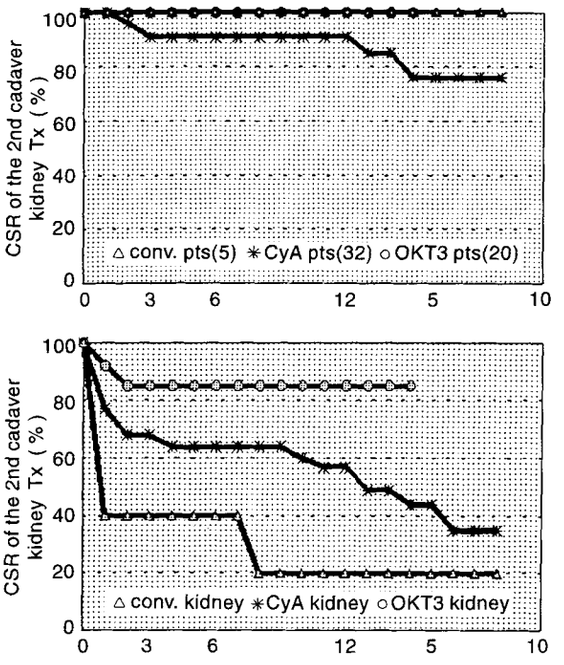

Fig. 1 Cumulative survival rate (*CSR*)

Table 1 Comparison of groups

	SIM-PRED $n = 32$	OKT3 + SIM-PRED $n = 20$	Significance
Age (years)	34.2 ± 9.6	35.2 ± 12.1	NS
Donor age (years)	32.7 ± 15.9	36.1 ± 13.9	NS
Donor creatinine (μmol/l)	119.1 ± 40.9	109.1 ± 28.2	NS
PRA (%)	18.6 ± 22.5	17.8 ± 30.8	NS
HLA-AB MM	1.7 ± 0.9	1.8 ± 0.5	NS
HLA-DR MM	1.2 ± 0.6	0.8 ± 0.6	$P < 0.05$
TIT (min)	1557.8 ± 381.3	1392.0 ± 213.5	NS
WIT (min)	0.6 ± 1.3	1.6 ± 2.3	NS
Blood transfusion (intraop)	2.1 ± 1.8	1.0 ± 1.4	$P < 0.05$
Dialysis time (months)	788.8 ± 656.6	933.1 ± 649.3	NS
Hospital stay (days)	24.8 ± 14.1	21.4 ± 11.6	NS
Blood transfusion (preop)	53.8 ± 49.8	42.6 ± 51.1	NS
Hb	5.5 ± 1.1	6.3 ± 0.9	$P < 0.01$
Se-creat.	818.6 ± 235.9	848.3 ± 119.0	NS
Se-K	5.1 ± 0.6	5.7 ± 0.8	$P < 0.01$
Se-Protein	76.5 ± 6.6	73.1 ± 6.5	NS
ApH	7.38 ± 0.06	7.41 ± 0.07	NS
St. Ricarb.	23.7 ± 4.3	23.8 ± 4.9	

Table 2 Results

	SIM-PRED $n = 32$	OKT3+SIM-PRED $n = 20$	Significance
Acute rejection < 30 days	15 (46.9%)	2 (10%)	$P < 0.05$
Acute rejection > 30 days	15 (46.9%)	6 (30%)	$P < 0.05$
Total rejections reversible	21	6	$P < 0.01$
1st	11	4	NS
2nd	2	1	NS
3rd	2	1	NS
Total rejections irreversible	9	2	NS
1st	6	2	NS
2nd	2	0	NS
3rd	1	0	NS
ATN	14 (43.7%)	4 (20%)	$P < 0.05$
Urine (ml)			
1st 24 h	3260±4757.0	3157±2894.7	NS
2nd 24 h	3124±4763.4	2573±2577.7	NS
Creatinine clearance ml/min			
1st 24 h	14.86±22.1	14.5±18.3	NS
2nd 24 h	10.72±17.9	12.9±17.2	NS
△ creatinine			
1st 24 h	4.16±27.8	8.6±21.9	$P < 0.05$
2nd 24 h	8.0±31.0	19.7±29.9	$P < 0.05$
Hospital stay (days)	24.9±14.1	21.4±11.6	NS
Early complication	18 (56.3%)	4 (28%)	$P < 0.01$

showed a difference in favour of the OKT3 group. The acute rejection rates within 30 days were significantly lower in the OKT3 group. The total number of rejections was significantly higher in the SIM + PRED groups (Table 2). Hospitalization time was shorter in the OKT3 group. Patient survival differed significantly after 4 years, but graft survival after 1 and 4 years was better in the OKT3 group (Fig. 1).

Discussion

The simultaneous use of SIM and OKT3 is not common [10, 13, 15, 18, 21]. Previously we have demonstrated that meticulously dosed SIM did not influence early kidney function (80% immediate function rate). Having observed relatively bad results after second kidney transplantations even using SIM, we decided to use OKT3 as prevention treatment in combination with SIM, with administration of both drugs starting before the transplantation. With this combination we wanted to assure strong immunosuppression and diminish the risk of antibody formation against the OKT3 molecule. This was later verified by different authors [4, 11–13, 16, 21, 25]. We found less ATN in the OKT3 group than has previously been reported [5, 20, 23]. Acute rejections occurred less frequently in the OKT3 group, confirming the findings of others [5, 17, 20]. The urinary volume in the first 2 days did not differ significantly but the creatinine clearance and the delta creatinine showed better early kidney function in the OKT3 group. No data about these parameters have been found in the literature, nor about length of hospital stay, which was shorter in the OKT3 group. The survival results clearly demonstrated the superiority of preventive treatment with OKT3 for the second kidney transplantation compared with SIM + PRED; with this therapeutic policy the second graft survival rate is nearly as good as for the first transplantation with simple SIM + PRED therapy.

The use of OKT3 as preventive treatment together with SIM + PRED for the second transplantation leads to a less frequent occurrence of ATN. It assures good early kidney function; significantly decreases the rejection rate within 30 days post-operation and the total post-transplant period; significantly decreases the rate of irreversible rejections with fewer complications and shortens the length of hospital stay. Much better patient and graft survival could be achieved with this treatment than in the control group. The 1- and 4-year graft survival is nearly as good as in the first kidney transplantation group with SIM + PRED treatment. We believe that preventive treatment using OKT3 with SIM + PRED is the immunosuppressive method of choice for the second kidney transplantations.

References

1. Calne RY, Rolles K, White DJG, Thiru F, Evans DB, McMaster P, Dunn DC, Craddock GN, Henderson RG, Aziz S, Lewis P (1979) Cyclosporin A intially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet II:1033
2. Canadien Multicentre Transplant Study Group (1983) A randomized clinical trial of cycosporine in cadaveric renal transplantation. N Engl J Med 309:809
3. Carey GP (1992) Benefits of prophylactic OKT3 therapy, OKT3 prophylaxis vs triple drug therapy. In: Monaco AP (ed) Roundtable report: Renal prophylaxis protocols. Boston, Massachusetts, pp 3–4
4. Cosimi AB (1981) The clinical value of antilymphocyte antibodies. Transplant Proc 13:462
5. Dafoe DC (1992) Identify patients in whome prophylactic OKT3 is particularly indicated. In: Monaco AP (ed) Roundtable report: Renal prophylaxis protocols. Boston, Massachusetts, pp 21–25
6. European Multicenter Trial Group (1983) Cyclosporin in cadaveric renal transplantation: one-year follow-up of a multicare trial. Lancet II:986
7. Goldstein G (1986) An overview: OKT3 of ortochlone OKT3. Transplant Proc XVIII:927–930
8. Hallora P, Aprile M, Farewell V, Ludwin D, Smith EK, Tsai SY, Bear RA, Cole EH, Fenton SS, Cattran DC (1988) Early function as the principal correlate of graft survival. A multivariate analysis of 2 cadaveric renal transplants treated with a protocol incorporating antilymphocyte globulin and cyclosporine. Transplantation 46:233
9. Halloran P, Aprile MA, Farewell V (1988) Factors influencing early renal function in cadaveric kidney transplants. A case control study. Transplantation 45:122
10. Hanto DW (1992) OKT3 prophylaxis therapy vs quadruple sequential therapy utilising polyclonal antilymphocyte globulin. In: Monaco AP (ed) Roundtable report: Renal prophylaxis protocols. Boston, Massachusetts, pp 5–8
11. Hardy MA, Nowygrod R, Elberg A, Appel G (1980) ATG in treatment of steroid-resistant rejection. Transplantation 29:162
12. Hayes JM (1993) The immunobiology and clinical use of current immunosuppressive therapy for renal transplantation. Urol 149:437–448
13. Hricik DR (1992) Identify and suggest improvements in concomitant therapy to minimize antibody formation and infectious complications. In: Monaco AP (ed) Roundtable report: Renal prophylaxis protocols. Boston, Massachusetts, pp 15–21
14. Kahan BD (1986) Cyclosporine nephrotoxicity: pathogenesis, prophylaxis, therapy, and prognosis. Am J Kidney Dis 8:323
15. Kreiss HA (1992) Identify modifications to improve cost-effectiveness and reduce first-dose morbidity. In: Monaco AP (ed) Roundtable report: Renal prophylaxis protocols. Boston, Massachusetts, pp 27–33
16. Light JA, Alijani MK, Biggers JA, Oddenin K, Reinmuth B (1981) Antilymphocyte globulin reverses irreversible allograft rejection. Transplant Proc 13:475
17. Monaco AP (1992) Introduction. In: Monaco AP (ed) Roundtable report: Renal prophylaxis protocols. Boston, Massachusetts, p 1
18. Norman DJ (1992) Identify new prophylactic protocols and potential new dosage regimens. In: Monaco AP (ed) Roundtable report: Renal prophylaxis protocols. Boston, Massachusetts, pp 9–13
19. North Italy Transplant Program (1988) Factors influencing cadaver kidney transplantation outcome in the cyclosporine era. In: Terasaki P (ed) Clinical transplants. UCLA Tissue Typing Laboratory, Los Angeles, pp 131–154
20. Ponticelli C, Rivolta E, Tarantino A, Egidi F, Banfi G, De Vecchi A, Montagnino G, Vegato A (1986) Clinical experience with orthoclone OKT3 in renal transplantation. Transplant Proc XVIII:942–948
21. Salomon DR (1991) The use of immunosuppressive drugs in kidney transplantation. Pharmacotherapy 11:153S–164S
22. Sommer BG, Henry M, Ferguson RM (1987) Sequential antilymphoblast globulin and cyclosporine for renal transplantation. Transplantation 43:85
23. Starzl TE, Fung JJ (1986) Orthoclone OKT3 in treatment of allograft rejected under cyclosporine-steroid therapy. Transplant Proc XVIII:937–941
24. Stratta RJ, D'Alessandro AM, Armbrust MJ, Pirsch JD, Sollinger HW, Lalayoglu M, Belzer FO (1989) Sequential antilymphocyte globulin/cyclosporine immunosuppression in cadaveric renal transplantation. Effect of duration of ALG therapy. Transplantation 47:96
25. Wechter WJ, Morrell RM, Bergan J, Rosenberg JC, Turcotte J, Shultz JR (1979) Extended treatment with antithymocyte globulin (ATGAM) in renal allograft recipients. Transplantation 28:365