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Abstract

A retrospective study was carried out in 110 cadaveric kidney transplant recipients to compare the effects of low doses of cyclosporine (CsA), azathioprine (AZP) and steroids (triple-drug therapy) with those of higher doses of steroids plus AZP (conventional immunosuppression). Graft survival rate in the triple-drug therapy was 77%, 69%, and 69% at 1, 3, and 5 years, respectively. This was significantly better than 48%, 34%, and 29% in conventional immunosuppression. The incidence of acute rejection episodes was significantly lower in the triple-drug therapy than in conventional immunosuppression (25% vs 58%). In conclusion, our study shows that triple-drug therapy using low-dose cyclosporine is the safest of the immunosuppressive regimens and provides a beneficial effect on the long-term survival of cadaveric kidney transplants.

KEYWORDS: cadaveric kidney transplantation, cyclosporine, triple-drug therapy

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The Impact of Triple Drug Immunosuppression on Clinical Results of Cadaveric Kidney Transplantation: A Comparison of Conventional Immunosuppression

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A retrospective study was carried out in 110 cadaveric kidney transplant recipients to compare the effects of low doses of cyclosporine (CsA), azathioprine (AZP) and steroids (triple-drug therapy) with those of higher doses of steroids plus AZP (conventional immunosuppression). Graft survival rate in the triple-drug therapy was 77 %, 69 %, and 69 % at 1, 3, and 5 years, respectively. This was significantly better than 48 %, 34 %, and 29 % in conventional immunosuppression. The incidence of acute rejection episodes was significantly lower in the triple-drug therapy than in conventional immunosuppression (25 % vs 58 %). In conclusion, our study shows that triple-drug therapy using low-dose cyclosporine is the safest of the immunosuppressive regimens and provides a beneficial effect on the long-term survival of cadaveric kidney transplants.

Key words : cadaveric kidney transplantation, cyclosporine, triple-drug therapy

The discovery of the immunosuppressive potency of cyclosporine A (CsA) by Borel (1), and its introduction into clinical organ transplantation by Calne (2), has led to a substantial improvement in kidney transplantation. In an attempt to maintain the improved immunosuppression provided by CsA and to reduce the incidence of CsA side effects, especially nephrotoxicity, triple-drug therapy with low doses of CsA, azathioprine (AZP), and steroids was introduced in 1985 (3, 4). The effects of triple-drug therapy on the long-term survival of cadaveric kidney grafts remains unclear. In this study, the long-term results associated with

cadaveric kidney transplants performed at our institution in which the recipients were treated with triple-drug therapy were compared to the results for similar transplants performed earlier using conventional therapy including AZP and methylprednisolone (MP).

All kidneys were retrieved from donors whose hearts had stopped beating. *In situ* cooling, en bloc nephrectomy and transplantation procedures were performed as previously described (5). This study consists of 110 cadaveric kidney's which were transplanted between February 1977 and March 1991. Recipients were classified into two groups according to the immunosuppressive regimen used: 1. Conventional therapy group. From February 1977 to October 1984, 38 recipi-

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ents received conventional immunosuppression with AZP and MP; and 2. Triple-drug therapy group. From November 1984 to March 1991, 72 patients received triple-drug therapy with low doses of CsA, AZP, and MP. In the conventional group, AZP was given at a dose of 1.5 to 2.5 mg/kg according to the white blood cell count. MP was given at an initial dose of 80 mg/day and tapered to 24 mg/day at 1-month post-transplant. From 6-month after transplantation, MP was given at a dose of 12 mg/day. In the triple-drug therapy group, CsA was given intravenously in a dose of 1.5 mg/kg for 24 h, beginning immediately after transplantation and then oral CsA administration with a initial dose of 6 mg/kg/day on the second day of surgery. This dose was reduced by 2 mg/kg every 2 weeks until a maintenance dose of 4 mg/kg was reached. During anuric period, CsA was maintained at a dose of 3 mg/kg/day. AZP was given at a dose of 50 mg/day. MP was given at an initial dose of 80 mg/day and tapered to 16 mg/day at 1-month after transplantation. From 6-month after transplantation, MP was given at a dose of 8 mg/day.

Actuarial allograft survival was calculated with the Kaplan-Meier method. Differences between the groups were determined by chi-square analy-

sis or by the t test. P values of < 0.05 were considered statistically significant. Nonsignificant difference are designated as NS.

The only important demographic difference between the two groups was variation in the ratios of male to female patients (Table 1).

The results are shown in Fig. 1. Graft survival for the patients in the triple-drug therapy was 77 %, 75 %, 69 %, 69 %, and 69 % at 1-4, and 5 years, respectively. This was significantly better when compared to 48 %, 39 %, 34 %, 29 %, and 29 % for patients in conventional immunosuppression ($p < 0.05$ at 1 year, and $p < 0.01$ at 2-4, and 5 years). Acute rejection episodes during the first 3 months were seen in 25 % of 72 cadaveric transplants received triple-drug therapy, compared with 58 % of 38 cadaveric transplants treated with conventional immunosuppression. This difference was statistically significant ($p < 0.05$). None of the 72 patients originally allocated to triple-drug therapy were changed to AZP and MP because of deteriorating renal function due to CsA-associated chronic nephrotoxicity.

The initial favorable experience with CsA in renal transplantation was reported by Calne *et al.* in 1978 (1), and large-scale, multicenter studies

Table 1 Patient characteristics^a

Immunosuppression groups	Conventional immunosuppression (AZP + MP)	Triple-drug therapy (CsA + AZP + MP)	P ^b
Number of patients	38	72	P < 0.05
Male/female	33/5	50/22	NS
Patients' age (years)	30.2 ± 7.2	37.8 ± 8.2	NS
Months on dialysis	27.2 ± 20.8	29.8 ± 25.6	NS
Cold ischemic time (h)	7.1 ± 2.7	7.8 ± 2.5	NS
HLA-A, B matches:	n = 38	n = 72	
0	27 %	28 %	NS
1-2	73 %	66 %	
3-4	0 %	6 %	
HLA-DR matches:	n = 15	n = 72	
0	53 %	24 %	NS
1	47 %	68 %	
2	0 %	8 %	

^a: Mean ± SD

^b: P < 0.05 was considered significant.

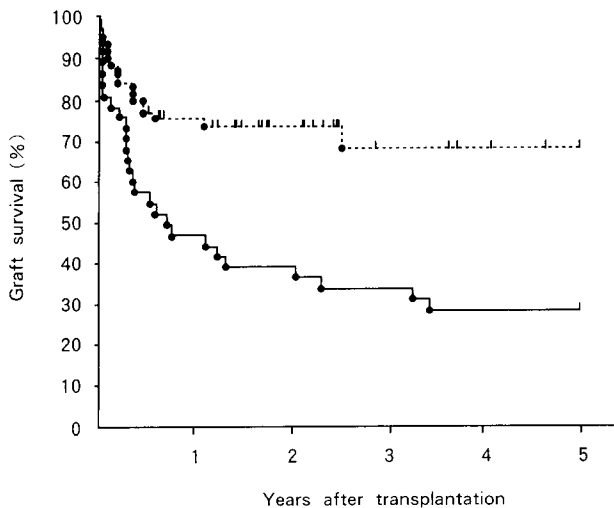


Fig. 1 Actuarial graft survivals according to different immunosuppressive modalities in cadaveric kidney transplantation. (●—●) triple-drug therapy group (n = 72), (●---●) conventional immunosuppression group (n = 38).

were commenced to evaluate the clinical role of CsA. In the European Multicenter Trial (6), CsA monotherapy was compared with conventional AZP-Steroid treatment in cadaveric kidney transplant recipients. CsA was associated with superior 1 year, 3 year, and 5 year graft survival (74 % vs 52 %, 66 % vs 42 %, and 55 % vs 40 %, respectively). In the Japanese cooperative study (7), CsA in combination with steroid (double therapy) was compared with historical control patients treated with AZP and steroid (conventional immunosuppression). One-year graft survival for CsA-treated group was significantly ($p < 0.001$) better than that for conventional immunosuppression (80.5 % vs 47.6 %). Because high doses of CsA (12–17 mg/kg/day) were often used in these studies, these CsA monotherapy or double therapy trials resulted in a high incidence of CsA-associated nephrotoxicity.

Our study shows an encouraging long-term outcome (69 % for 5-year graft survival) for recipients of cadaveric renal grafts treated with triple-drug therapy using low-dose CsA (at a initial dose of 6 mg/kg/day). Several articles (3,

4, 8–10) have reported that a triple-drug regimen, with the addition of AZP to CsA and steroids, can allow a reduction of CsA dosage without reducing immunosuppressive efficacy. This might prevent the side effects of CsA given in full doses, especially nephrotoxicity. The results achieved by these combination protocols have in general been excellent (3, 4, 8–10). In Minneapolis (8), CsA-AZP-steroid and AZP-steroid-ALG were studied in cadaveric kidney recipients. The 1-year actuarial graft survival was 82 % for CsA-AZP-steroid, and 77 % for AZP-steroid-ALG. These new combination regimens showed a low prevalence of rejection episodes (8, 9) and a low incidence of CsA-nephrotoxicity (10).

In conclusion, our study indicates that triple-drug therapy using low-dose cyclosporine is the safest form of immunosuppressive regimens at the present time and provides a beneficial effect on the long-term survival of cadaveric kidney transplants. Furthermore, we believe that the best results when using this combination therapy may be achieved by maximizing the AZP, utilizing low-dose maintenance CsA, and gradually phas-

ing out the steroid so that triple-drug therapy becomes double-drug therapy with only AZP and CsA.

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References

1. Borel JF: Comparative study of *in vitro* and *in vivo* drug effects on cell mediated cytotoxicity. *Immunology* (1976) **31**, 631-641.
2. Calne RY, White DJG, Thiru S, Evans DB, McMaster P, Dunn DC, Craddock GN, Henderson RR, Aziz S and Lewis P: Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* (1979) **ii**, 1033-1036.
3. Slapak M, Geoghegan T, Digard N, Ahmed K, Sharman VL and Crockett R: The use of low-dose cyclosporine in combination with azathioprine and steroids in renal transplantation. *Transplant Proc* (1985) **17**, 1222-1226.
4. Fries D, Kechrid C, Charpentier B, Hammouche M and Moulin B: A prospective study of a triple association: Cyclosporine, corticosteroids, and azathioprine in immunologically high-risk renal transplantation. *Transplant Proc* (1985) **17**, 1231-1234.
5. Sakagami K, Takasu S, Kawamura T, Saito S, Haisa M, Oiwa T, Kurozumi Y, Hasuoka H, Inagaki M, Niguma T, Shiozaki S, Tanaka S and Orita K: A comparison of University of Wisconsin and Euro-Collins' solutions for simple cold storage in non-heart-beating cadaveric kidney transplantation. *Transplantation* (1990) **49**, 824-826.
6. Calne RY: Cyclosporin in cadaveric renal transplantation: 5-year follow-up of a multicentre trial. *Lancet* (1987) **ii**, 506-507.
7. Ochiai T, Toma H, Takagi H, Oka T, Ishibashi M, Kashiwabara H, Fukao K, Ota K, Hashimoto I, Sonoda T and Iwasaki Y: Japanese multicenter trial of Cyclosporine in renal transplantation: Over all results and analysis of the factors influencing graft survival rate. *Transplant Proc* (1987) **19**, 2961-2966.
8. Simmons RL, Canafax DM, Fryd DS, Ascher NL, Payne WD, Sutherland DER and Najarian JS: New immunosuppressive drug combinations for mismatched related and cadaveric renal transplantation. *Transplant Proc* (1986) **18**, 76-81.
9. Brinker KR, Dickerman RM, Gonwa TA, Hull AR, Langley JW, Long DL, Nesser DA, Trevino G, Veles RL and Vergne-Marini PJ: A randomized trial comparing double-drug and triple-drug therapy in primary cadaveric renal transplants. *Transplantation* (1990) **50**, 43-49.
10. Landsberg DN, Rae A, Chiu A, Werb R, Taylor P, Chan-Yan C and Manson AD: The use of triple therapy to minimize cyclosporine (CsA) nephrotoxicity in renal transplantation. *Transplant Proc* (1989) **21**, 1550-1551.

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