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Triple therapy immunosuppression in cadaveric renal transplantation

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Abstract. One hundred and ninety-two patients received 200 consecutive cadaver renal transplants (158 first and 42 regrafts) and were treated with triple therapy immunosuppression consisting of low-dose cyclosporin, azathioprine and prednisolone. One-year patient and graft survival rates were 95% and 82%, respectively. Against this low rate of graft loss, the proportion of rejection-free patients in the first 3 months was strongly related to matching for HLA-DR ($P < 0.01$), although HLA-DR matching was not associated with improved graft survival. More grafts were lost to nonimmunological causes than to rejection, and these losses fell into three main categories, namely, losses in elderly and diabetic patients and losses due to renal vascular thrombosis. Thus, triple therapy immunosuppression appears to offer effective immunosuppression, resulting in good graft and patient survival, especially in highly sensitised patients or patients receiving regrafts. There are relatively few serious adverse effects, although elderly and diabetic patients experienced significant morbidity and mortality after transplantation.

Key words: Immunosuppression, triple therapy, kidneys – Cyclosporin, in triple therapy – Azathioprine, in triple therapy – Kidney transplantation, triple therapy.

Early clinical trials with cyclosporin in renal transplantation, used alone or together with steroids, demonstrated a significant improvement in allograft survival, but the use of cyclosporin was associated with significant nephrotoxicity [3, 8, 20]. Although the nephrotoxicity appeared to be reversible, at least in the short term [4, 19, 21], many units have explored the use of multidrug regimens with lower doses of cyclosporin in an attempt to reduce the incidence of the adverse effects of each of the drugs used, while maintaining the immunosuppressive advantages of cyclosporin. Triple therapy, comprising low doses of cyclosporin, azathioprine and prednisolone, was one such regimen introduced by several groups [10, 14, 31] that has become widely accepted as an immunosuppressive regimen.

Despite the widespread use of triple therapy, only one randomised controlled trial comparing triple therapy with single or double drug regimens has been reported [26]. This study showed that both triple therapy and double therapy with cyclosporin and steroids were associated with similar 1-year graft survival rates. However, in patients receiving triple therapy, there were fewer serious infections and less cyclosporin-associated nephrotoxicity. In addition, there is experimental data showing that cyclosporin and azathioprine have additive or possibly synergistic immunosuppressive effects [33]. Our own initial experience with triple therapy [15] confirmed that this was an effective immunosuppressive regimen that was relatively free of side effects. In this report we have examined the outcome of the first 200 cadaver transplants treated with triple therapy, with particular reference to the matching of donor and recipient.

Patients and methods

Triple therapy with cyclosporin, azathioprine and prednisolone has been used as routine immunosuppression in Oxford since May 1985. By the end of June 1988, triple therapy had been given to 192 adult recipients of 200 consecutive cadaver renal transplants. Patient characteristics are shown in Table 1.

One hundred and seventy-five kidneys were retrieved locally and 25 were received via the United Kingdom Transplant Service. Recipients were preferentially selected for transplantation on the basis of HLA-DR matching. All recipients were given preoperative cefuroxime (1.5 g intravenously). Routine peroperative care included central venous pressure monitoring and the intravenous administration of frusemide 80 mg, mannitol 12.5 g and hydrocortisone 100 mg immediately prior to release of the vascular clamps.

Immunosuppression consisted of azathioprine at a dose of 1.5 mg/kg and prednisolone 20 mg, administered at least 4 h preoperatively and daily thereafter. Gradual reduction of the dose of prednisolone to 10 mg/day was begun at 90 days after transplantation. The dose of azathioprine was reduced if the total peripheral leukocyte count fell below 4.0×10^9/l. Cyclosporin was given in-

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Table 1. Patient characteristics in 192 recipients of 200 cadaver grafts

Characteristic	Number
Number of grafts	200
Male:female	124:76
Mean age (range)	40.2 (17–66)
Number over 55 years	50 (25%)
Regrafts	42 (21%)
Highly sensitised patients	
First grafts	11 (7%)
Regrafts	21 (50%)
Positive crossmatch patients	
First grafts	19 (12%)
Regrafts	27 (64)%
Mean total cold ischaemic time (min)	1356 (SD 347)

Table 2. Patient and graft survival

	Survival (%)				
Group	Number	3 months	6 months	1 year	2 years
Patient	192	97	96	95	95
All grafts	200	84	83	82	78
First grafts	158	85	84	82	78
Regrafts	42	79	79	79	76

travenously at a dose of 4 mg/kg per day for the first 4 days and thereafter orally at a dose of 10 mg/kg per day, except for the first 45 patients who were given oral cyclosporin only. The dose of cyclosporin was adjusted according to whole blood trough cyclosporin levels. These were measured using a polyclonal radioimmunoassay (Sandoz) with a therapeutic range of 400–800 ng/ml for the first 6 weeks and 200–400 ng/ml thereafter.

Rejection was diagnosed according to clinical and laboratory criteria, most often when a rise in plasma creatinine was accompanied by a fall in urine output and occasionally graft tenderness and fever. Rejection was confirmed by biopsy or by cytological examination of fine needle aspirates. Biopsies were routinely performed at 7, 21, 28, 90 and 365 days after transplantation in the first 158 patients, and at 7, 14, 21, 28 and 90 days after transplantation in the last 42 patients. Rejection was treated in the first instance with 500 mg intravenous methylprednisolone daily for 3–5 days (250 mg daily in patients weighing less than 60 kg more recently).

Rejection was defined as steroid-resistant if there was no response to methylprednisolone within 7 days of starting treatment, in which case a course of rabbit antithymocyte globulin (ATG, Fresenius, Munich, FRG) at a dose of 2–4 mg/kg per day for 5–10 days was given.

Highly sensitised patients were defined as those having cytotoxic antibodies reactive with 90% or more of a panel of peripheral blood lymphocytes and/or a panel of lymphocytes from patients with chronic lymphocytic leukaemia. Highly sensitised patients and those with a current positive or a previous positive-current negative crossmatch were given 500 mg intravenous methylprednisolone daily for the first 3 days.

Primary function after transplantation was defined as the passage of greater than 1500 ml of urine in the first 24 h, associated with a fall in plasma creatinine levels with no need for dialysis in the 1st week. Complications after transplantation were recorded at routine weekly mortality and morbidity meetings. The cause of any patient death or graft loss was entered onto a prospectively compiled computer database, and a record was kept of all admissions to hospital and the nature of any complications.

Statistical analysis was performed by chi-squared tests (Minitab, Pennsylvania State University, 1982).

Results

The mean follow-up period for the 155 grafts still functioning at the end of June 1989 was 26.8 months (range 8–46 months). Details of the patients and of survival rates are shown in Tables 1 and 2.

Patient survival

The actuarial patient survival at 1 year was 95% (Tables 2, 3). All 11 deaths occurred in patients receiving their first grafts. There was a significant difference in 1-year patient survival between first graft recipients aged 55 years or older and those under 55 years of age (84% versus 97%, $P = 0.0012$). Comparison of first graft recipients in this instance was made because all those aged 55 years or older were receiving first grafts.

Graft survival

The actuarial 1-year graft survival for the entire group was 82%. There was no significant difference between graft survival in first graft recipients (82%) or in second or subsequent graft recipients (79%; Table 2). Although the effect of HLA-DR matching on overall graft survival appeared to be beneficial, this did not reach statistical significance (Fig. 1a). Figures 1b and 1c show the relationships between graft survival and matching for HLA-DRw 52/53 and HLA-DQ, respectively, and again there is a suggestion of a beneficial effect of matching for HLA-DRw 52/53. No influence of HLA-A, B or C matching on graft outcome was noted (data not shown). The causes of graft loss are summarized in Table 4, and it is of interest that more than half of the graft losses were considered to be due to nonimmunological causes.

Highly sensitised patients

Thirty-two highly sensitised patients were transplanted, with a 1-year graft survival rate of 78.1% (with at least 1 year of follow-up in each patient). Of the seven grafts that were lost, five failed due to rejection and two patients

Table 3. Causes of death in 11 patients

Transplant number	Age (years)	Time after transplantation	Cause of death
699	66	Day 1	Ruptured abdominal aortic aneurysm
659	42	Day 1	Myocardial infarction
657	62	Day 36	Pulmonary embolism
626	62	Day 43	Respiratory arrest
713	67	Day 40	Myocardial infarction
554	59	Day 47	Pancreatitis
649	64	3 months	Hypoglycaemia (?insulin overdose)
682	58	5 months	Miliary tuberculosis
545	29	10 months	*Pseudomonas* septicaemia
594	56	36 months	Hypertrophic cardiomyopathy
508	51	41 months	Postoperative pulmonary embolism

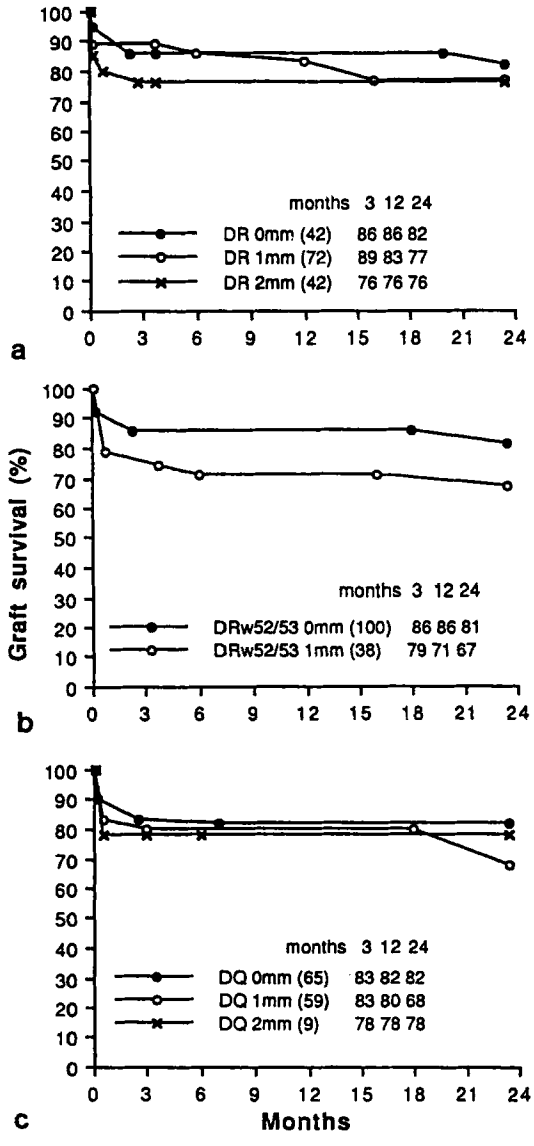

Fig. 1 a–c. Graft survival in first cadaver transplants according to: **a** HLA-DR mismatches ($P = 0.1562$); **b** HLA-DRw52/53 mismatches ($P = 0.0782$); **c** HLA-DQ mismatches ($P = 0.2477$)

died with functioning grafts. Of the 11 highly sensitised patients receiving their first graft, only 1 was lost, compared to 6 of 21 in regrafted patients. All the graft losses occurred in the first half of this series, and each of the last 17 highly sensitised patients transplanted has a functioning graft.

Positive crossmatches

Transplantation was performed in the presence of a positive crossmatch in 46 patients. The crossmatch was due to autoreactive antibodies in 23 patients, due to HLA antibodies in old but not current sera in 12, and probably due to autoreactive antibodies in 11 (but not fully proven by laboratory testing). Twenty-nine of these patients were also highly sensitised. Thirty-six (78.2%) of these grafts are still functioning. Graft losses were due to rejection

Table 4. Causes of graft failure in 200 consecutive transplants over a follow-up period of 8–46 months

Cause of graft loss	Number
Rejection in first 6 months	15
Rejection after 6 months	4
Death	11
Primary renal vein thrombosis	6
Technical[a]	4
Tuberculosis	2
Recurrent glomerulonephritis	1
Other	2
Total	45

[a] These failures comprised poorly preserved kidney from another centre that never functioned ($n = 1$), renal artery and vein thrombosis secondary to: hypotension postoperatively ($n = 1$), hypotension during dialysis ($n = 1$), and heavily calcified iliac artery and difficult arterial anastomosis ($n = 1$)

($n = 5$), patient death with functioning graft ($n = 3$) and vascular thrombosis ($n = 2$). Within this group graft survival was related to the specificity and subclass of the antibody causing the positive crossmatch; the results in these patients have recently been included in a much larger analysis from our centre [36].

Graft function

The primary function rate was 72% for the entire group, and of the 56 grafts that did not achieve primary function, 32 (57%) eventually functioned. There was no significant difference between the primary function rates for first grafts (73%) and regrafts (69%). The mean plasma creatinine level in all patients with functioning grafts was 152 (SD 54) µmol/l at 12 months. The mean plasma creatinine level in the 32 patients whose grafts functioned after delayed function was 162 (SD 34) µmol/l at 12 months, which was not statistically different from that of the entire group.

Rejection

If patients with early graft failure due to nonimmunological causes are excluded, 45 of 187 patients (24%) had no rejection episodes. In the 142 patients who did experience rejection, there were 294 episodes (a mean of 2.1 per pa-

Table 5. Proportions of rejection-free patients according to HLA DR, DRw52/53 and DQ matching. The beneficial effect of DR matching was highly significant ($P < 0.01$)

HLA type and number of mismatches		Number of patients	Number (%) with no rejection episodes
HLA-DR	0 mm	36	16 (44.4%)
	1 mm	64	16 (25%)
	2 mm	32	5 (15.6%)
HLA-DRw52/53	0 mm	86	27 (31.4%)
	1 mm	30	6 (20.0%)
HLA-DQ	0 mm	54	18 (33.3%)
	1 mm	50	14 (28.0%)
	2 mm	7	2 (28.6%)

Table 6. Infectious complications requiring hospitalization

Type of infection	Number of patients
Major	
Septicaemia	5
Tuberculosis	4
Pneumonia	
Bacterial	2
Pneumocystis carinii	3
Intra-abdominal abscess	1
Wound infection	4
Cytomegalovirus	6
Herpes zoster	4
Urinary tract infection	4
Epididymo-orchitis	2
Pyrexia of unknown origin	1
Total	38
Minor	
Perianal abscess	2
Urinary tract infection	4
Bronchitis	1
Cytomegalovirus	7
Gastroenteritis	3
Cellulitis	2
Pyrexia of unknown origin	2
Total	21

tient), and the mean dose of methylprednisolone given to each patient was 2.75 g (range 0.75–6.5 g).

There were 132 first graft recipients whose grafts functioned for at least 3 months and in whom HLA-DR typing of both donor and recipient was fully performed. There was a significant relationship between HLA-DR matching and the proportion of patients who had no rejection episodes (Table 5). A similar analysis for HLA-DRw52/53 and HLA-DQ matching showed no significant influence, although there were considerably more patients with no rejection episodes in the patients matched for HLA-DRw52/3.

Thirty-eight patients suffered from steroid-resistant rejection (19% of the total). Nine of these patients received no further immunosuppression and lost their grafts. The reasons for withholding further immunosuppression were: concurrent pneumonia ($n = 1$), renal vein thrombosis and allograft rupture ($n = 1$), accelerated rejection with no postoperative function ($n = 3$), patients with previous failed grafts who had already received large doses of immunosuppression ($n = 2$), and patient refusal ($n = 1$). Twenty-nine patients with biopsy-proven, steroid-resistant rejection were treated with ATG, with subsequent recovery of graft function in 21 cases (72.4%).

Complications

There were 38 major infectious episodes in 34 patients (17%) and 21 minor episodes in 19 patients (9.5%; Table 6). Four of the major infections – two septicaemias and two cases of cytomegalovirus (CMV) infection – occurred in patients who had received ATG.

There was an outbreak of *Pneumocystis carinii* pneumonia in 1985, occurring in 3 of the first 25 patients in this series and also in two others. All five patients recovered with oral or intravenous high-dose cotrimoxazole, and none required assisted ventilation. Prophylactic cotrimoxazole (480 mg once daily for the first 6 months) has been administered routinely since 1985, and no further cases of *Pneumocystis* pneumonia have been seen. We have recently described the other possible adverse and beneficial effects of this prophylaxis [12].

There were four cases of tuberculosis. Two occurred in patients who had spent many years living on the Indian subcontinent, and the other two patients were both insulin-dependent diabetics, one of whom had been exposed to tuberculosis when her sister died 40 years previously, while the other had lived 36 years previously in an area where tuberculosis was endemic. One patient developed a tuberculous empyema and recovered uneventfully. The other three all had miliary tuberculosis with serious complications, despite prompt diagnosis by bronchoscopy and treatment with triple drug antituberculous chemotherapy. One patient died from a combination of metabolic disturbance and hepatic failure, and the other two patients lost their grafts from rejection. This followed withdrawal of immunosuppression either because of life-threatening infection or because of interactions with cyclosporin.

There were six serious CMV infections, all of which occurred in seronegative patients receiving kidneys from seropositive donors. One of these serious infections was associated with a pneumonitis and hypoxia, but assisted ventilation was not necessary. The incidence and severity of CMV disease may have been modified by the use of a live, attenuated CMV vaccine in seronegative recipients [25]. This vaccine has been used by us in a multicentre, randomised, controlled trial since March 1986; the trial is still in progress. The case of Guillain-Barré syndrome (Table 7) followed a CMV infection and is described in detail elsewhere [7].

Other noninfectious complications (not included in Table 3, which describes causes of graft loss) are shown in Table 7. All three lymphocoeles required percutaneous needle drainage due to either leg swelling with deep vein thrombosis or an effect on renal function, or both. Two of these patients subsequently required surgical drainage by intraperitoneal fenestration, as the lymphocoele continued to accumulate despite repeated needle drainage. Three patients developed a ureteric stenosis; one has been treated surgically, the other two with ureteric stenting.

Twelve patients whose renal failure was due to diabetes received renal transplants. Patient and graft sur-

Table 7. Complications either occurring in the early postoperative period or requiring admission to hospital, which are not included in Tables 3 or 5

Complication	Number of cases
Reoperation for postoperative bleeding	6
Renal artery stenosis	4
Lymphocoele	3
Ureteric stenosis	4
Stroke	2
Guillain-Barré syndrome	1
Iliac artery occlusion	1

vival rates at 1 year were 84% and 67%, respectively, and all of the losses occurred in patients over the age of 40 years.

Discussion

The reported results of second or subsequent renal grafts and the transplantation of highly sensitised patients have generally continued to be significantly worse than those for nonsensitised first graft recipients [5, 34]. A striking feature of our results with triple therapy is that there was no significant difference between overall 1-year graft survival in these groups. This good graft survival in these potentially high-risk patients may be due not only to improved immunosuppression but also to a better understanding of the interpretation of positive crossmatch tests [36]. It should be noted that our good results in regrafts and highly sensitised patients are not due to avoiding transplantation in these patients; 21% of the transplants in this series were regrafts, 16% were in highly sensitised patients, and 23% of the patients had a positive crossmatch in either current or old serum. Attempts to improve graft survival in highly sensitised patients simply by administering more immunosuppression – for example, the use of quadruple therapy – do not necessarily improve graft survival and may, in fact, increase patient mortality [34].

Although only 7.5% of the grafts were lost from rejection in the 1st year, 19% of the patients experienced steroid-resistant rejection episodes. In the 29 cases treated with ATG, there was a success rate of 72%. We have recently examined in detail the results of ATG treatment in these patients. The response to treatment was not associated with either the severity of rejection at renal biopsy or plasma creatinine levels before starting treatment. The mean 1-year plasma creatinine level in those successfully treated was the same as in patients who experienced no rejection in the first 3 months [28].

While graft loss due to rejection has become less important, graft loss due to nonimmunological causes and patient death in this series was greater than that due to rejection. The three major causes were death of elderly (over 55 years of age) and diabetic patients and renal vascular thrombosis.

Many units throughout the world transplanted progressively older patients during the 1980s [24]. Analysis of results from Oxford shows that patients over 55 years of age have a higher mortality than younger patients, but that graft survival is similar [17]. As many elderly patients may tolerate the rigours of dialysis poorly, transplantation appears to be the treatment of choice in these patients, at least up to the age of 70 years.

Twelve (6%) of the patients in this series had renal failure caused by diabetes mellitus. The 1-year patient and graft survival rates in this small group of patients were 84% and 67%, respectively. These results are similar to those reported by other units [22, 29, 38], although some recent results are better [35]. It is notable that cadaver transplantation does not appear to extend the survival of diabetic patients when compared with dialysis treatment [2, 13, 16, 38]. As older diabetic patients and those with vascular disease are at greatest risk of death [22, 29], transplantation might not be performed in these patients if there is an acceptable quality of life on dialysis.

There have been some conflicting reports as to whether matching donor and recipient for HLA-DR antigens remains beneficial in the cyclosporin era [18]. In our series the effect on overall graft survival is modest, although a beneficial effect continues to be reported from large international registries [6, 23, 37]. However, the effect of matching for HLA-DR is particularly striking when the proportions of rejection-free patients are examined (Table 5) and may be clinically important when the adverse effects of high-dose steroid and other treatments for rejection are taken into account. Thus, we are continuing to endeavour to match for HLA-DR antigens in clinical practice and, since January 1989, we have participated in the United Kingdom Transplant Service scheme for organ sharing in an attempt to improve HLA matching both locally and nationally.

HLA-DQ antigens are expressed on kidney cells and are upregulated in rejecting grafts [11]. The effect of HLA-DQ matching in clinical transplantation has, thus, been of interest for some time, but it has been difficult to study because of the linkage disequilibrium between HLA-DR and HLA-DQ [9] and also because the polymorphisms of HLA-DQ have only recently been determined in detail [27]. Both this study and other data from our unit [1] show that HLA-DQ has no major effect on renal allograft survival or function, and we do not take account of HLA-DQ matching in the selection of renal allograft recipients.

Although the benefits of HLA-DRw52/53 matching did not reach statistical significance with regard to either graft survival or rejection episodes, there was a trend in favour of a beneficial effect, which warrants further study in larger series.

What of future immunosuppressive regimens? Some units use quadruple therapy, routinely administering prophylactic ATG or OKT3 in addition to triple therapy, while others use sequential therapy, delaying the introduction of cyclosporin in an attempt to reduce the impact of cyclosporin nephrotoxicity on primary renal function [30, 32]. We do not use these protocols in Oxford for two reasons. First, the primary function rate in this series was 72%, so that there seems no need to routinely avoid administering cyclosporin in the 1st week after transplantation. Secondly, we wish to avoid giving unnecessarily powerful immunosuppression to our patients, particularly as nearly half of the patients receiving HLA-DR compatible grafts went on to experience no acute rejection. It is still not clear whether triple therapy is the best long-term immunosuppressive regimen, and we are currently addressing this question with a randomised trial.

In conclusion, triple therapy immunosuppression gave an overall 95% patient and 82% graft survival at 1 year in 200 consecutive cadaver transplants. Nonimmunological causes accounted for more than half of all graft losses. While the transplantation of highly sensitised patients and regrafts was associated with good results, elderly and diabetic patients, not surprisingly, had a high incidence of serious complications.

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