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Cyclosporin A

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Cyclosporin A and steroid treatment in 104 cadaveric renal transplantations

THOMAS E. STARZL, THOMAS R. HAKALA, SHUNZABURO IWATSUKI, THOMAS J. ROSENTHAL, BYERS W. SHAW Jr., GORAN B. G. KLINTMALM and KENDRICK A. PORTER

Department of Surgery, University of Pittsburgh Health Sciences Center, Pittsburgh, PA 15261, U.S.A. and Department of Pathology, Saint Mary's Hospital and Medical School, London, U.K.

1. Introduction

Published clinical accounts of the use of Cyclosporin A (CyA) in renal transplantation have recorded a remarkable discordance of results. Calne et al. (1978, 1979a,b, 1981a,b) and we (Starzl et al., 1980, 1981a,b) have become enthusiastic proponents of CyA whereas the experiences at the Royal Free Hospital, London (Sweny et al., 1981) and The Peter Bent Brigham Hospital, Boston (Carpenter et al., 1981) have been disappointing. Problems with drug toxicity have prompted recommendations that CyA treatment be restricted to those recipients who have an established postoperative diuresis (Calne et al., 1979a,b, 1981a,b) or that doses be regulated by sophisticated pharmacologic and immunologic monitoring (Keown et al., 1981; Rynasiewicz et al., 1981; Kahan et al., 1981). An unresolved controversy has been whether to use CyA as the sole drug as Calne et al. have recommended (1978, 1979a,b, 1981a,b) or to combine it with steroid therapy from the outset as we have suggested (Starzl et al., 1980, 1981a,b). This communication will focus on these practical questions, based upon our experience in treating 104 cadaveric renal recipients.

2. Graft and patient survival

2.1. Colorado series

66 patients were treated from 12 to 21 months ago. Donor-recipient matching was random. Deliberate preoperative transfusion was not done. Diabetics and other poor risk patients were included.

9 (13.6%) of the recipients died from 20 to 335 days postoperatively. A detailed account of these deaths has been published (Starzl et al., 1981b). In brief, three failures were from cardiovascular complications not related to immunosuppression and

six were caused or contributed to by over immunosuppression with resulting infections. At autopsy, one of the latter patients was found to have a monoclonal B cell lymphoma (Starzl et al., 1981b).

7 patients were changed from CyA to azathioprine after 4–13 months, because of suspected nephrotoxicity (5 examples), hepatotoxicity (one example) or toxicity of both organs (1 example). Two of the grafts were rejected after 2 and 10 weeks, and the other 5 have continued to function (usually at an improved level) for 4 weeks to more than a year.

Only 3 of 50 patients who still have grafts have serum creatinine concentrations ≥ 3 mg% and their function has been stable between 3 and 4.5 mg%.

Systematic biopsies were not obtained, but through autopsy, nephrectomy, or biopsy, studies were made of 12 of the 16 lost grafts of which most have been reported (Starzl et al., 1981b). Two of the examined kidneys were normal or nearly normal, nine had acute and/or chronic rejection and one had been destroyed by recurrent oxalosis. There were no findings attributable to CyA toxicity. A search for the large mitochondria described by Mihatsch et al. (1981) in patients under CyA therapy has not been made. An increased number of eosinophiles in the cellular infiltrate was the only unusual finding.

2.1.1. Primary cadaveric transplantation (57 cases)

In this learning period the actual one year graft survival was 45/57 (79%). An additional graft in a non-compliant patient was lost to rejection after 14 months. Thus, 44 (77.2%) of the original 57 grafts are still functioning 12–21 months (Fig. 1). These results were markedly better than in an old (1976–1977) series of patients treated with azathioprine and prednisone, with or without a short course of ineffective ALG, at the same institution (Fig. 1).

2.1.2. Cadaveric retransplantation (9 cases)

Ten kidneys were placed into nine recipients. One was removed because of complete ureteral necrosis, and another graft was placed 6 weeks later. Therapy was stopped in three other patients because of a lung abscess, a bleeding duodenal ulcer, and a deep wound infection. A few days, or weeks later, their transplanted kidneys were removed.

Six (67%) of the nine recipients have good renal function after 14–21 months. Graft survival is 6/10 (60%).

2.2. Pittsburgh series

38 patients were treated with CyA one to 6 months ago, 21 with primary grafts and 17 with second or third grafts. Their mean age was 33.3 ± 13.1 (S.D.) years, range 8–64. All primary recipients were given at least three preoperative transfusions. Diabetics and other poor risk candidates were included. An attempt was made at donor–recipient matching, but this was only marginally successful. The HLA matches averaged 1.3 ± 1.3 (S.D.), and only 7 kidneys were placed which were matched for three

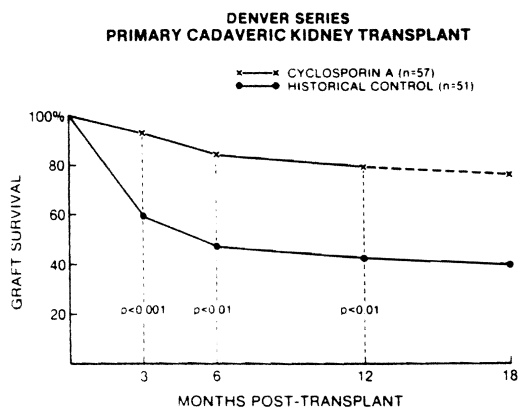


Fig. 1. Actual one year survival of 57 primary cadaveric renal grafts at the University of Colorado. Followup is 12–21 months. Historical controls are from 1976–77 in whom treatment was with azathioprine and prednisone, with or without what proved to be homeopathic ALG.

or four HLA antigens. In 13 cases, there were no antigens matched. DR matching was random.

12 of 38 patients had antibodies against more than half of a screening lymphocyte panel, and in seven of these cases the reactivity was against > 90% of the panel and was accounted for mostly by T warm cytotoxic antibodies. Three fourths of the recipients with preformed antibodies were in the retransplantation group. In four cases (all but one in the retransplantation group) stored recipient sera as recent as four weeks completely killed donor lymphocytes, although the crossmatches with sera drawn on the day of operation were negative. In many centers, the latter finding is interpreted as a positive crossmatch and precludes transplantation.

There have been no deaths. The only potentially serious complication was *Pneumocystis carinii* pneumonia which was effectively treated with antibiotics. None of the patients were permanently switched from CyA to azathioprine, although this change was made for a few days as a therapeutic trial in two patients.

Only one of the 34 recipients still bearing grafts has a serum creatinine concentration greater than 3 mg% (the exception is 3.6 mg% and improving.) The average creatinines in the primary cadaveric and retransplantation series are given in Table 1.

Pathologic examination of the four grafts which were removed showed infarction in two (due to one example each of early renal artery and renal vein thrombosis) and acute and chronic rejection in the other two. The patient with renal vein thrombosis had received an ABO incompatible kidney. Needle biopsies of three other grafts were obtained because of uncertainty of diagnosis. Two contained mild or moderate signs of acute rejection. One had mild glomerulitis.

2.2.1. Primary cadaveric transplantation (21 cases)

A kidney from a donor of 'A' blood-type underwent infarction after accidental transplantation to a recipient of 'O' blood-type. The other 20 (95.2%) are functioning (Table 1). The ABO incompatibility was an inadvertent violation of the agreed upon protocol, and if this case is thereby excluded the graft survival is 100% (Fig. 2).

TABLE 1: University of Pittsburgh series (follow-up is 1-6 months)

	No.	Kidneys lost	Deaths	Average creatinine (mg%) (range)
Primary	21	1*	0	1.6 (0.9-2.5)
Retransplantation	17	3**	0	1.9 (1.2-3.6)

* ABO incompatibility by administrative error.

** 2 rejections; one renal artery thrombosis (technical error).

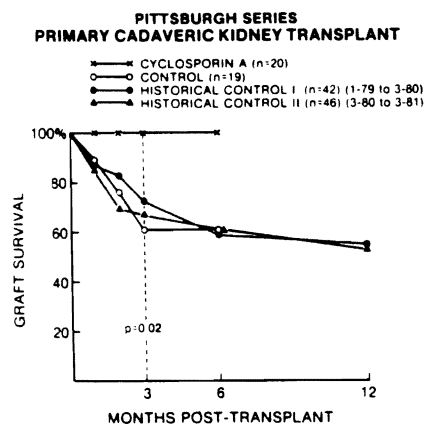


Fig. 2. Actuarial survival in University of Pittsburgh primary cadaveric kidney recipients treated with CyA and steroids versus azathioprine and prednisone. For the azathioprine-prednisone patients, historical (1979-80) as well as contemporaneous controls are shown. An additional kidney in the CyA group was excluded from analysis because of an administrative accident in which an A blood-type kidney was transplanted to an O blood-type recipient.

A contemporaneous trial was conducted of primary cadaveric transplantation in 19 patients under azathioprine-prednisone. There have been no deaths. The trial was randomized except for a few patients in each group. Six (32%) of the azathioprine group have lost their grafts and one other has a serum creatinine concentration of 5.5 mg%. The early results of graft survival on this control group are almost

identical to those achieved with prednisone the preceding trial.

The divergence between the two control groups is so striking that continuing randomization

2.2.2. Cadaveric retransplantation

One of the 17 cadaveric retransplants (one error) and two more kidneys are now functioning well. The results after retransplantation in an eighteenth patient who lost a first kidney from hypoparathyroidism. He

Concomitant azathioprine plantations were performed. Grafts had been rejected

3. Steroids, CyA ne

In the earlier Colorado trial the first patients were prednisone and one with peripheral neuropathy. CyA for days or weeks and then often given in combination resulted. It was not to be expected early in those of CyA nephropathy seen by Calne et al. the frequency of rejection. A therapeutic program (Starzl et al., 1981) without resorting to damage to the new kidney, and to achieve pharmacologic monitoring it may seem, the 1 valuable for eventual a variety of other or

In the following recently treated Pittsburgh therefore provided

identical to those achieved by the University of Pittsburgh team with azathioprine-prednisone the preceding two years.

The divergence between the test and either the contemporaneous or historical control groups is so striking (Fig. 2) that it has raised questions about the probity of continuing randomization.

2.2.2 Cadaveric retransplantation

One of the 17 cadaveric grafts was lost to an early renal artery thrombosis (technical error) and two more kidneys were lost to rejection. 14 (82.3%) of the transplants are now functioning well, after one to six months. The difficulty of achieving these results after retransplantation is discussed later. By prior compassionate agreement, an eighteenth patient was not considered part of this study since she had previously lost a first kidney from oxalosis which could not be effectively treated because of hypoparathyroidism. Her second graft was even more promptly ruined by oxalosis.

Concomitant azathioprine-prednisone controls were not obtained. 13 retransplantations were performed at Pittsburgh in the preceding two years. 7 (54%) of these grafts had been rejected by the end of the third postoperative month.

3 Steroids, CyA nephrotoxicity and management

In the earlier Colorado CyA series, treatment was in no sense standardized. Ten of the first patients were pretreated with lymphoid depletion (nine by thoracic duct drainage and one with peripheral lymphopheresis). A number of patients were pretreated with CyA for days or weeks. Steroid therapy was withheld initially after transplantation and then often given sporadically or so overzealously that several deaths from infection resulted. It was soon evident that significant and sometimes severe rejection often could be expected early or late and that confusion of these immunologic events with those of CyA nephrotoxicity could account in part for the eventual poor renal function seen by Calne et al. (1979b) in the majority of his first patients. Biopsy proof of the frequency of rejection under CyA therapy was provided by Carpenter et al. (1981). A therapeutic program was suggested (Starzl et al., 1980, 1981a) and standardized (Starzl et al., 1981b). The regimen was designed to minimize diagnostic confusion without resorting to routine biopsy or other instrumentation, to prevent permanent damage to the new kidney, to avoid jeopardizing the patient with overimmunosuppression, and to achieve these ends without the kinds of sophisticated immunologic and pharmacologic monitoring which is available in only a few centers. Mundane though it may seem, the last objective will be an important determinant in making CyA valuable for eventual widespread clinical use in transplanting not only the kidney but a variety of other organs as well.

In the following account will be described the evolution of early recovery in the recently treated Pittsburgh patients who were all treated uniformly at first and who therefore provided data about the incidence of necessary deviation from a recipe

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approach. For this analysis, the two patients will be excluded who lost their kidneys from an ABO compatibility breach and from a renal artery thrombosis due to a surgical error. Of the 36 remaining patients, 20 were primary cadaveric recipients and 16 were undergoing retransplantation.

3.1. Standard CyA-steroid therapy

The therapeutic program enacted is simple (Fig. 3). CyA is given orally in a dose of 17.5 mg/kg, 3–4 h before transplantation, hoping to achieve a good therapeutic level by the time the new organ is vascularized. The practice is consonant with the pharmacokinetic data of Beveridge et al. (1981) which showed peak plasma levels of CyA 4 or 6 h after ingestion. 24 h postoperatively the same amount is given, by mouth, in virtually every patient since postoperative ileus necessitating a parenteral route is rare after renal transplantation. Thereafter, the daily dose of 17.5 mg/kg is divided, half being taken every 12 h. If there is no subsequent reason to change, the same daily dose is continued.

The steroid component of therapy is also preplanned. Just before or during operation, 1 g of methylprednisolone is given intravenously. Afterwards, the patient is given a five day course of prednisone, starting at 200 mg/day with reductions of

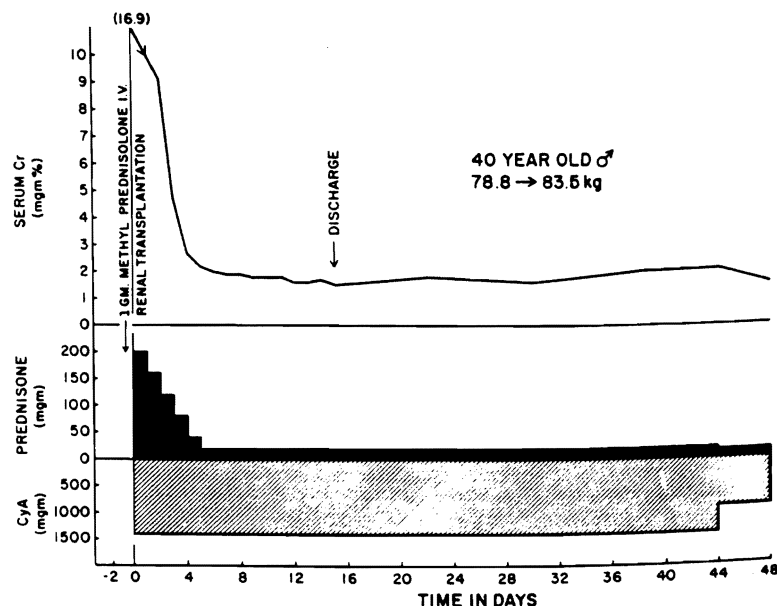


Fig. 3. Benign convalescence under CyA-prednisone therapy (Class I, see text).

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40 mg/day each day until on the fifth postoperative day the dose is 40 mg. On the sixth day, the dose is reduced to a maintenance level of 20 mg (Fig. 3). The same steroid schedule is used for all adults without consideration of body weight, but for smaller children the peak dose is started at 100 mg. and the maintenance dose is also gauged lower.

3.1.1. Uncomplicated recovery (Class I)

If convalescence is untroubled, the patient is discharged in 10–15 days. In a few weeks, the prednisone can be dropped further (Fig. 3) and after 2 months it can be reduced in many adults to 10 mg/day.

A day or two after operation a renal flow scan is obtained with Tc 99m DTPA or some other appropriate isotope. The radionuclide studies can give important inferential information if a differential diagnosis becomes necessary between rejection and CyA nephrotoxicity. In addition, the graft is examined with ultrasound to provide a baseline in the event of later trouble.

In 13 (36.1%) of the 36 patients, deviations from this early plan were not necessary. In the outpatient clinic, the CyA dose was eventually lowered to approximately 10 mg/kg/day (Fig. 3) if there was delayed evidence of renal or liver toxicity, or if lesser complications such as hirsutism, gum hyperplasia, discoordination or abdominal discomfort after ingestion of the drug caused patient complaints. Delayed nephrotoxicity and hepatotoxicity were indolent in onset and mild in expression as has been described by Klintmalm et al. (1981a,c) from the earlier Colorado experience. A serum creatinine concentration of 2–3 mg% did not cause alarm and often did not lead to a dose change until the end of two months, if then. A normal or near normal renal flow scan at this time provided assurance of the correctness of the decision since good flow in conjunction with stable but reduced renal function is most compatible with CyA nephrotoxicity (Starzl et al., 1980; Klintmalm et al., 1981b).

3.2. Deviations from standard

3.2.1. Acute renal failure after initial function (Class II)

After having initial diuresis, 20 (55.5%) of the 36 patients developed a secondary decline of renal function (Table 2), usually suddenly (Figs. 4 and 5). The crises occurred from a few hours, to two weeks postoperatively, and in 11 cases required temporary return of the patient to dialysis (Fig. 5). Close attention to urinary output allowed the diagnosis to be made before blood chemistry results were available. Wound tenderness, graft swelling, and fever were common as previously described (Starzl et al., 1980).

The complication was treated immediately as a rejection (Figs. 4 and 5). One gram of hydrocortisone was given intravenously and the six day burst of prednisone therapy used initially was repeated (Figs. 4 and 5), sometimes stopping the stepdown at 30 mg/day whether or not an unequivocal therapeutic response was obtained (Fig. 5). In most of these patients 450 rad irradiation at depth was delivered in three doses of

TABLE 2: Evolution of recovery after 36 cadaveric renal transplantations in Pittsburgh (Class I up 1-6 months)

	Features of class	No.	Good outcome
Class I	Uneventful recovery	13 (36.1%)	13/13
Class II	Acute deterioration of early function	20 (55.5%)*	18/20
Class III	Anuria at outset	3 (8.3%)	3/3

* 5 of these patients had an initial significant diuresis which began to shut down within a few hours; most would have been excluded from CyA therapy if a 6 or 12 h urine output of 50 ml/h were required.

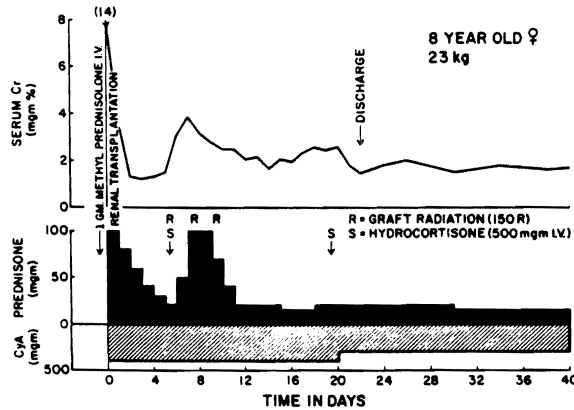


Fig. 4. Class II recovery, with secondary deterioration of graft function which was immediately responsive to increased steroid therapy. The clinical diagnosis was rejection.

150 rad every other day (Figs. 4 and 5). Some of the patients were treated with low doses of heparin.

Initial diagnostic steps were few and non-invasive. Ultrasound examination was obtained to rule out perinephric fluid collection and ureteral obstruction. If radio-nuclide scans showed poor renal blood flow, the best diagnosis was considered to be rejection (Stables et al., 1979). Good renal blood flow, at this time, was considered compatible with either a rejection with an excellent prognosis, or CyA nephrotoxicity.

In most recipients, CyA doses were not immediately adjusted (Fig. 4), particularly if there was a good therapeutic response to the steroid therapy. Definite and quick steroid response was observed in 13 of the 20 patients with this syndrome, leading to the conclusion that rejection had occurred. If prompt and complete reversal was not obtained, and if repeat scans showed maintenance of good renal blood flow, the strong

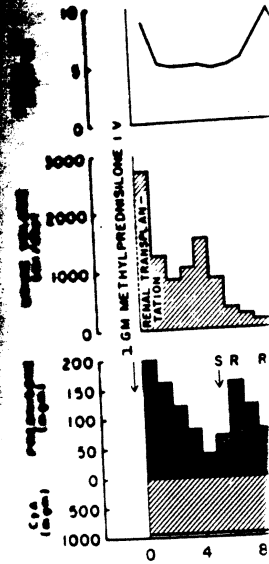


Fig. 5. Class II recovery with rejection in CyA dose. The angiogram showed narrowing of the distal vessels. The biopsy result was good.

possibility of acute rejection dropped to 10 mg/kg and was not increased above a reasonable (if not low) dose.

Failure to see a response to steroid therapy promoted further diagnostic steps (2 cases), and in both kidneys had some evidence of rejection and if the renal biopsy showed rejection with 10 mg/kg of CyA and prednisone to which a response was seen in 4 of the 6 patients. In 2 cases, CyA dose reduction was necessary. The two grafts which showed chronic rejection. The patient died before giving up.

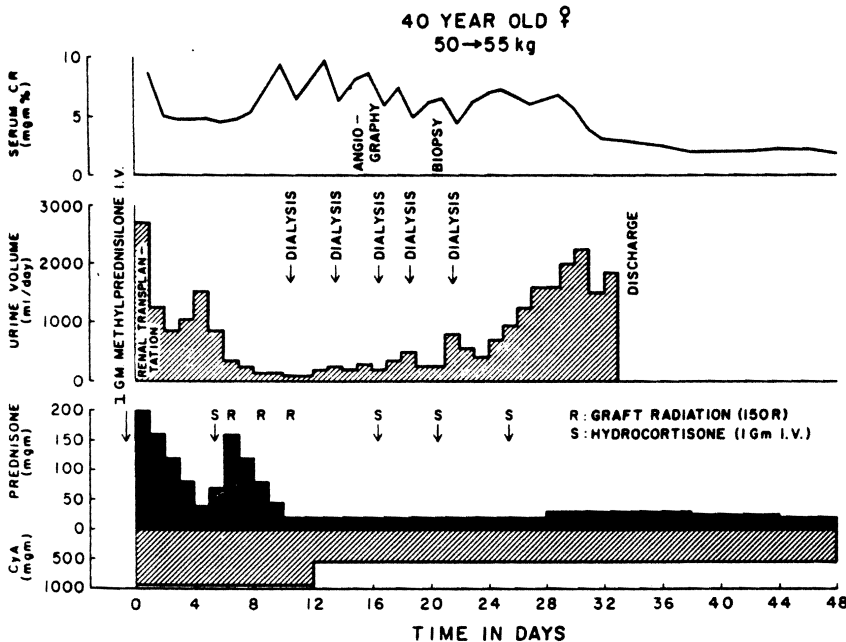


Fig. 5. Class II recovery which was not promptly responsive to steroid therapy, prompting a reduction in CyA dose. The angiogram showed a patent arterial system with a 'stripped tree' appearance of the distal vessels. The biopsy showed glomerulitis. Although oliguria was prolonged, the eventual result was good.

possibility of acute CyA nephrotoxicity was entertained. Daily CyA doses were dropped to 10 mg/kg or occasionally lower (Fig. 5). Maintenance steroid doses were not increased above 30 mg/day and usually they were kept at 20 mg/day. With the reasonable (if not low) daily prednisone doses the patients were not ill.

Failure to see a response to both of the foregoing drug manipulations (6 examples) promoted further diagnostic procedures (Fig. 5) including biopsy (5 cases), angiography (2 cases), and retrograde ureteral catheterization (2 cases). All of the biopsied kidneys had some evidence of rejection. If no mechanical problems could be found, and if the renal biopsy did not show irreversible damage, daily therapy was continued with 10 mg/kg of CyA or less and maintenance prednisone doses of 20–30 mg prednisone to which a 1 g dose of hydrocortisone was added every fourth or fifth day. 4 of the 6 patients who did not respond clearly either to steroid burst therapy or to CyA dose reduction finally achieved satisfactory function 2½–5 weeks postoperatively. The two grafts which were eventually removed had irreparable damage from acute and chronic rejection. These last two patients were kept on dialysis for 3 and 11 weeks before giving up.

3.2.2. Immediate anuria (Class III)

The grafts of three recipients did not function at once (Fig. 6) requiring postoperative dialysis 2–5 times. Usually, it was known in advance that there had been long warm ischemia times, or that the flow characteristics were suboptimal in those suspect kidneys that had been preserved by perfusion. Only one of the three recipients was considered before operation, to be at immunologic jeopardy from widely reactive T warm cytotoxic antibodies and retransplantation.

For Class III patients, standard therapy was followed (Fig. 6). All three recipients recovered in the usual way after an ATN and were thereafter managed the same way as Class I patients.

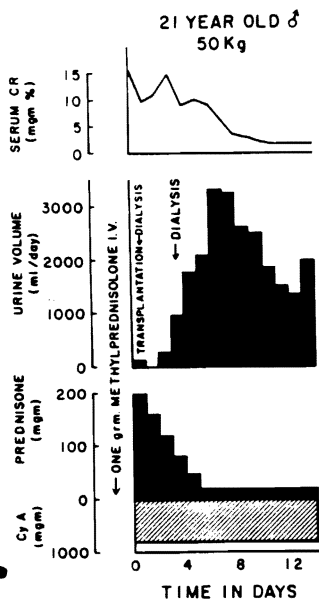


Fig. 6. Class III convalescence with immediate anuria. The graft was from a 13-year-old donor and had warm ischemia for an unknown time (estimated 20–60 min) before cooling with Collins' solution. Therapy with CyA and prednisone was by the standard schedule.

3.2.3. Relation of classes of recovery and retransplantation

The predominance of Class I patients was in the 20 recipients of primary grafts (Table 3). Amongst the recipients of primary grafts, the most difficult course was of a woman whose current serum had T warm antibodies against >90% of a lymphocyte panel and whose recently stored sera reacted against donor cells. Her kidney became anuric within a few hours, but eventually recovered.

The high incidence of Class II early renal failure after retransplantation was additional evidence for a major immunologic factor in these troublesome but eventually manageable patients. If diuresis had been a necessary condition to begin CyA as in the

TABLE 3: Primary versus

	T
Primary grafts	20
Retransplants	10

reported experience of most in need of superior We (Starzl et al., 1980) of selection.

4. Immunologic an

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A statement cannot be obtained too late to It is logical to agree manifestations of Cy but in future clinical simpler guide to app Some of our patients 1000 ng/ml and other levels.

5. Discussion and

On the basis of information possible advances in years ago. Even during veric graft survival in tion was not far behind due mainly to inexpl therapeutic interaction w survivors that graft t will be prohibitive.

TABLE 3: Primary versus retransplantation and quality of convalescence

	Total	Class I (sustained function)	Class II (secondary graft failure)	Class III (immediate anuria)
Primary grafts	20	9 (45%)	9 (45%)	2 (10%)
Retransplants	16	4 (25%)	11 (69%)	1 (6%)

reported experience of Calne et al. (1979b, 1981a,b), it seems likely that the patients most in need of superior immunosuppressive therapy would have been screened out. We (Starzl et al., 1980, 1981b) and Rynasiewicz et al. (1981) have not used this criterion of selection.

4. Immunologic and pharmacologic monitoring

Drs. Paul Terasaki and Yuichi Iwaki of the University of California, Los Angeles, carried out serial immunologic tests in the majority of the Colorado cases. Plasma levels of CyA were performed in selected early patients at the University of Minnesota and in later cases at the University of Pittsburgh.

A statement cannot be made now about the results except to say that they were obtained too late to influence clinical management early or late after transplantation. It is logical to agree with Keown et al. (1981) and Kahan et al. (1981) that toxic manifestations of CyA will be accompanied by elevated plasma and blood CyA levels, but in future clinical practice, an equally sensitive, more directly relevant and far simpler guide to appropriate dosage, could be the toxic manifestations themselves. Some of our patients have had no complaints despite trough levels of CyA as high as 1000 ng/ml and others with perfect renal function have had scarcely detectable peak levels.

5. Discussion and Conclusions.

On the basis of information already available, it seems certain that CyA will make possible advances in transplantation which were barely conceivable only two or three years ago. Even during an awkward learning period the actual one year primary cadaveric graft survival in our hands was nearly 80%, and the record with retransplantation was not far behind. A 13.6% patient mortality, mostly in the first months, was due mainly to inexperience with CyA and an imperfect understanding of its therapeutic interaction with steroids. Later, there has been little evidence from the chronic studies that graft failures will occur late at a rapid rate or that other complications will be prohibitive. One lymphoma was seen in the first 67 patients. Another lympho-

proliferative reaction which caused an intestinal perforation after a bout of infectious mononucleosis was judged by a number of consultants to be benign (Starzl *et al.*, 1981b). No other lymphomas have been seen in 71 other recipients of livers, hearts and kidneys treated by us with CyA and steroids.

Applying hard earned lessons in a fresh series, the early mortality has been eliminated with an even higher primary (approaching 100%) and retransplantation graft survival. The conservative use of steroids with CyA from the time of transplantation has allowed protection of graft function and has allowed stepwise adjustments of both agents to be a keen diagnostic tool with the main criteria of diagnosis being the therapeutic response to change. However, effective treatment has not depended on early graft function. The monitoring of immunologic and pharmacologic parameters will undoubtedly yield interesting information but sound clinical management does not hinge on such techniques.

The rapid and sometimes simultaneous drug adjustments in Class II and III patients accommodated both of the possibilities of rejection and CyA nephrotoxicity and thus a final inferential diagnosis often could not be made. In any given case, it is not necessary to assume that postoperative renal dysfunction is attributable solely to rejection or CyA nephrotoxicity. Both factors could and probably do contribute. The concept probably is particularly important for treating patients who start with, or who develop intractable oliguria. In such cases, the luxury is lost of correlating graded drug changes with therapeutic response. From our experience, it is clear that both rejection and nephrotoxicity can be treated by simultaneously increasing steroids and reducing CyA.

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