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Renal allograft immunosuppression

VI. Triple drug therapy versus immunosuppressive double drug combinations: histopathological findings in renal allografts

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Abstract. The long-term effects of different immunosuppressive drugs and regimens on renal allograft histology are virtually unknown. Therefore, in order to investigate the long-term effects of triple drug treatment versus different combinations of two immunosuppressive drugs on allograft histology, a prospective, randomized trial was performed. One group received triple therapy consisting of low-dose cyclosporin (CyA), azathioprine (Aza), and methylprednisolone (MP), and three groups received combinations of two drugs, i.e., Aza plus CyA, Aza plus MP, and CyA plus MP. At 2 years, there were no significant differences with regard to graft (80%) or patient (87%) survival, or to graft function between the four groups. After 2 years, a protocol core biopsy was taken of all 102 patients having a functioning graft. Of these patients, 61 (60%) were still following the original, randomized treatment protocol; in the remaining cases, changes had occurred in the original protocol and so these cases were considered drop-outs in this study. Histological specimens were examined blindly by two independent observers. Most of the 34 histological variables examined showed no changes. Diffuse fibrosis was most frequent in the CyA plus MP group (70%) and significantly more severe than in the triple therapy group. Mesangial matrix increase in glomeruli was significantly less common in the triple therapy group (8%) than in any one of the double drug combination groups (47%). Two other changes in glomeruli – Bowman capsular thickening and global glomerular sclerosis – were also less frequent in the triple therapy group. Vascular changes other than intimal proliferation (39%) and arteriosclerosis (24%) were uncommon in all groups and least frequent in the triple therapy group. Isometric vacuolation in proximal tubules was found in every group using CyA. It was least prominent in the triple therapy group and most prominent in the CyA plus MP group; it was not seen in the Aza plus MP group. Other specific findings for the groups treated with CyA could not be identified. To summarize, the changes shown were mild and rather similarly distributed in the four treatment groups. Histopathological alterations comparable with chronic rejection, i.e., persistent interstitial inflammation with pyroninophilic cells, vascular intimal proliferation, and arteriosclerosis, were seen in all groups, but these changes were least prominent in the group receiving triple therapy.

Key words: Triple drug therapy, kidney transplantation – Immunosuppression, kidney transplantation

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Since the introduction of cyclosporin (CyA), the short-term results of kidney transplantation have dramatically improved. However, over the years, long-term graft survival rates have not improved to a corresponding degree in contrast to 1-year rates [20].

The principal difficulty in successful renal transplantation is no longer acute rejection but the prevention of chronic rejection. There is limited histological data available as to which immunosuppressive regimen is superior to all others in the prevention of chronic rejection. Furthermore, criteria to distinguish chronic CyA nephrotoxicity from chronic rejection are far from clear and the histological features may be overlapping [17]. The extent of histopathological lesions of renal allografts has most often only been reported in cases where the graft function has already deteriorated [5, 18], and no morphological study employing different immunosuppressive treatment protocols and protocol biopsies for chronic lesions exists as yet.

We performed a prospective, randomized trial comparing triple drug therapy consisting of CyA, azathioprine (Aza), and methylprednisolone (MP) with any of the possible double drug combinations. At 2 years, no one of the different modes of treatment was clearly superior with regard to graft or patient survival or to graft function. A protocol core biopsy was taken of all functioning grafts 2 years after transplantation in order to compare the histological features of grafts when using different immunosuppressive therapies. This analysis included all patients who had followed the original, randomized treatment

Table 1. Data of four treatment groups at the time of biopsy 2 years after transplantation. Values indicate mean ± SD

	Treatment group			
	Triple therapy	Aza + CyA	Aza + MP	CyA + MP
Number of patients following original treatment schedule	14	12	12	23
Representative biopsies	13	11	10	20
Number of glomeruli	6.4 ± 3.0	8.6 ± 4.7	5.9 ± 2.1	7.1 ± 3.6
Donor age (years)	37 ± 16	33 ± 17	40 ± 14	35 ± 13
Recipient age (years)	46 ± 10	53 ± 8	47 ± 12	46 ± 13
Mean serum creatinine (μmol/l)	128 ± 51	126 ± 47	137 ± 50	144 ± 69
Median serum creatinine (μmol/l)	115	115	118	113
CyA concentration (ng/ml[a])	85 ± 52	112 ± 46	–	104 ± 36
CyA dose (mg/kg per day)	3.1 ± 1.4	3.3 ± 1.8	–	3.2 ± 1.1
Aza dose (mg/kg per day)	0.9 ± 0.3	1.2 ± 0.6	1.8 ± 0.5*	–
MP dose (mg/kg per day)	0.05 ± 0.02	–	0.10 ± 0.05*	0.06 ± 0.03
Number of antirejection therapies per patient during first 6 months	0.29	0.17	0.25	0.30

* $P < 0.001$; other differences not significant
[a] Whole blood with monoclonal RIA

over a 2-year period. Changes compatible with experimental studies and previous histological evidence of chronic rejection were studied to determine whether any one of the four different modes of immunosuppressive treatment was more efficacious in preventing chronic allograft damage than any other. The omission of CyA in one of the treatment groups made it possible to evaluate whether there were any specific CyA-related changes when low-dose CyA regimens were employed.

Patients and methods

Clinical data/patients

The clinical details of this study have already been reported [8]. Originally, 128 consecutive patients with a first cadaveric renal graft were randomized into four different treatment groups 10 weeks after transplantation. The initial immunosuppression during the first 10 weeks was triple therapy, i.e., low-dose CyA, low-dose MP, and Aza. After 10 weeks one group continued with triple therapy while the three other groups received different combinations of two drugs, i.e., Aza plus CyA, Aza plus MP, and CyA plus MP. Randomization resulted in four similar groups. There were no significant differences in age, sex ratio, cold ischemia time, pretransplant transfusions, HLA-mismatches, or panel-reactive antibodies [8]. After 2 years, 102/128 (80%) patients had functioning grafts and 61/102 (60%) patients were still following the original, randomized mode of treatment. At 2 years there were no significant differences in graft or patient survival or in graft function between the four groups. Two-year graft and patient survival rates were 80% and 87%, respectively. The most common reasons for drop-outs were azathioprine intolerance and mild rejections during conversion when MP or CyA was discontinued [7]. CyA was added to immunosuppression in those patients. Thus, the number of patients following the original schedule was lower in the groups using azathioprine, and not because of CyA discontinuation.

Informed consent was obtained and at 2 years a core biopsy was taken of all grafts without contraindications. Since the purpose was to evaluate histological changes under different immunosuppressive treatment protocols, only patients who had followed the original randomized treatment were included in this study. There were 14, 12, 12, and 23 patients following the original treatment in the triple therapy, Aza plus CyA, Aza plus MP, and CyA plus MP groups, respectively, and representative biopsies were available from 13, 11, 10, and 20 patients, respectively. A biopsy was regarded as representative if it included at least five glomeruli. Seven out of 61 patients who followed the original, randomized treatment did not have adequate biopsies: two specimens were without glomeruli, two patients had contraindications for biopsy, and three specimens were invalidated because of technical problems while processing the samples. Thus, this study group consisted of 54 patients who had followed the original treatment after randomization for 2 years and in whom a biopsy was representative (Table 1).

At 2 years the CyA dose was identical for every group, i.e., 3 mg/kg per day. The doses of Aza and MP were equal in different

Table 2. Parameters evaluated in the histological specimens of renal grafts. All specimens were coded and histopathological changes were scored semiquantitatively from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe)

Interstitium[a]	Glomeruli
Inflammation	Number of glomeruli
Lymphocytes	Mesangial cell proliferation
Neutrophils	Mesangial matrix increase
Macrophages	Capillary basement membrane thickening
Eosinophils	Capillary basement membrane duplication
Pyroninophilic cells	Capillary thrombosis
Edema	Bowman capsular thickening
Hemorrhage	Glomerular inflammation
Fibrin deposits	Glomerular sclerosis
Fibrosis	Glomerular necrosis
Tubuli[b]	**Vessels[c]**
Epithelial swelling	Endothelial swelling
Epithelial vacuolation, isometric	Endothelial proliferation
Epithelial vacuolation, anisometric	Intimal proliferation
Epithelial atrophy	Inflammation
Necrosis	Sclerosis
Casts	Obliteration
Inflammation	
Dilatation	
Basement membrane thickening	

[a] Diffuse and focal changes
[b] Proximal and distal tubules
[c] Arteries, arterioles, and veins

groups, but the Aza plus MP group received twice the dosage of each drug as those having CyA in their regimen.

Biopsy technique and analysis

Percutaneous needle core biopsies were taken with an ultrasound-guided, automated punch device (Biopty-Cut, Radiplast, Bromma, Sweden). A needle of 1.2 mm (outer diameter) was used that yielded biopsies of 0.9 × 20 mm [10]. The biopsy was performed only after coagulation variables were found to be adequate. There were no biopsy-related complications. All biopsies were fixed in 4% formaldehyde and embedded in paraffin. Serial 4-μ thin sections were stained using routine hematoxylin and eosin, Masson's trichrome, Unna-Pappenheim (= methylgreen-pyronin), periodic acid-Schiff (PAS), and methenamine silver PAS methods for light microscopic examination.

The samples were coded and examined by two independent observers who had no knowledge about the treatment or of the clinical data of the patients. The biopsy was considered adequate if it contained at least five glomeruli. The mean number of glomeruli was 7 with a maximun of 19 glomeruli. Histopathological changes were scored semiquantitatively from 0 to 3, with 0 = none, 1 = mild, 2 = moderate, and 3 = severe. In every biopsy several different parameters in interstitium (focal and diffuse), glomeruli, vessels (arteries, veins, and arterioles), and tubuli (proximal and distal) were scored separately. The examined morphological features are listed in Table 2.

Statistical analysis

For the evaluation of normally distributed values between the four groups, an analysis of variance (ANOVA) was used, and for the intensity of histological changes, the Kruskall-Wallis test was used. For absolute numbers of the four groups, a contingency table or Fischer's exact test was used when appropriate. For testing the correlation between histological changes and clinical parameters such as graft function, donor age, and doses of immunosuppressive treatment, the Spearman rank correlation test was used.

Results

Comparison of renal histology between four different treatment groups

In most of the variables examined, no changes were demonstrated. In general, the histological findings were distributed rather similarly within the four different treatment groups. The intensity of the most common changes per patient per group are presented in Table 3. There were only two histological features for which the frequency of the changes differed significantly in the four treatment groups (Fig. 1).

Interstitium. The histopathological features were classified as focal (less than two out of four visual fields) or diffuse. The majority of biopsies had some degree of focal cellular infiltration. Focal infiltrations were more common than diffuse ones. Focal inflammation was similar in each treatment group and was present in 57% of the biopsies. In most cases it was mild. In these infiltrates lymphocytes predominated; focal pyroninophilic cells were seen in 22% of the biopsies and other cells only infrequently. There were no significant differences in focal fibrosis between the four different groups, something which was present on the average in 30% of all grafts.

Table 3. Intensity of histopathological features in different immunosuppressive treatment groups. Values indicate mean score per patient per group ± SE

	Triple therapy	Aza + CyA	Aza + MP	CyA + MP	Kruskal-Wallis corrected *P*
Intersititium, diffuse					
Inflammation	0.1 ± 0.1	0.3 ± 0.2	0.4 ± 0.3	0.4 ± 0.2	0.907
Lymphocytes	0.1 ± 0.1	0.3 ± 0.2	0.4 ± 0.3	0.3 ± 0.2	0.658
Pyroninophilic cells	0.0 ± 0.0	0.1 ± 0.1	0.4 ± 0.2	0.2 ± 0.1	0.400
Fibrosis	0.2 ± 0.1*	0.5 ± 0.2	0.8 ± 0.3	1.1 ± 0.2	0.051
Intersititium, focal					
Inflammation	0.6 ± 0.2	0.6 ± 0.2	0.3 ± 0.1	0.8 ± 0.2	0.499
Lymphocytes	0.6 ± 0.2	0.5 ± 0.2	0.3 ± 0.1	0.8 ± 0.2	0.379
Pyroninophilic cells	0.3 ± 0.2	0.3 ± 0.2	0 ± 0	0.4 ± 0.2	0.310
Fibrosis	0.5 ± 0.2	0.4 ± 0.2	0.5 ± 0.3	0.2 ± 0.1	0.512
Glomeruli					
Mesangial matrix increase	0.1 ± 0.1	0.5 ± 0.2	0.3 ± 0.1	0.5 ± 0.1	0.161
Bowman capsular thickening	0.1 ± 0.1	0.2 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.189
Glomerular sclerosis	0.3 ± 0.1	0.7 ± 0.3	0.6 ± 0.3	0.5 ± 0.1	0.751
Vessels					
Intimal proliferation	0.3 ± 0.2	0.4 ± 0.2	0.3 ± 0.1	0.7 ± 0.2	0.238
Sclerosis	0.1 ± 0.1	0.3 ± 0.2	0.2 ± 0.1	0.4 ± 0.2	0.295
Tubuli					
Epithelial swelling	0.3 ± 0.2	0.2 ± 0.1	0.5 ± 0.2	0.4 ± 0.1	0.386
Isometric vacuolation	0.3 ± 0.2	0.1 ± 0.2	0 ± 0	0.1 ± 0.1	0.353
Anisometric vacuolation	0.4 ± 0.4	0.4 ± 0.1	0.6 ± 0.2	0.4 ± 0.1	0.856
Tubular atrophy	0.5 ± 0.1	0.8 ± 0.2	1.0 ± 0.3	0.8 ± 0.2	0.512
Basement membrane thickening	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.6 ± 0.2	0.083
Tubular dilatation	0 ± 0	0.2 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.819

* $P < 0.05$, triple therapy versus CyA + MP

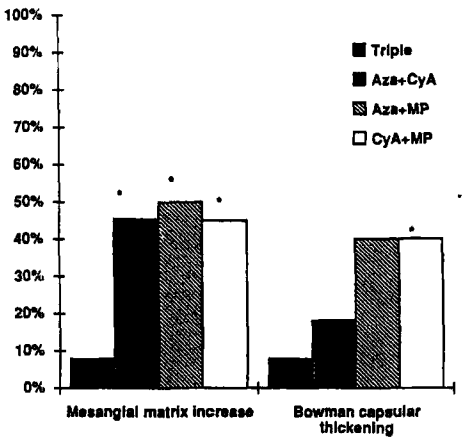

Fig. 1. Significant difference in the frequency of the histological changes seen only in mesangial matrix increase and Bowman capsular thickening of glomeruli. $*P < 0.05$ when compared with triple therapy (Fischer's exact test)

Diffuse cellular infiltration was least prominent in the triple therapy group. Diffuse pyroninophilic cells were seen in 30% of the Aza plus MP group and in 8%–15% of the groups using CyA. Diffuse fibrosis was most frequent in the CyA plus MP group (70%) and most uncommon in the triple therapy group (38%). In the CyA plus MP group, the intensity of fibrosis was significantly greater than in the triple therapy group ($P < 0.05$). The intensity of diffuse fibrosis was, however, mild in all groups and mostly related to glomerular abnormalities, especially to mesangial matrix increase and glomerular sclerosis.

Focal fibrosis did not correlate with tubular atrophy, but diffuse fibrosis did correlate with tubular atrophy ($r = 0.50$, $P = 0.0003$). Graft function correlated with diffuse fibrosis but not with focal fibrosis. All grafts with impaired graft function (serum creatinine > 200 μmol/l) had diffuse fibrosis with tubular atrophy. Diffuse fibrosis with tubular atrophy was similar in each of the four treatment groups; there were no significant differences.

Glomeruli. There were three main changes. Mesangial matrix increase was found in 8% of the grafts in the triple therapy group and, on the average, in 47% of the biopsies from patients receiving any of the double drug combinations ($P < 0.05$ when compared with triple therapy). Bowman capsular thickening was most common in the CyA plus MP and Aza plus MP groups (40%) but was rare in the triple therapy group (8%). Glomerular sclerosis (global) was found in all groups (39% of biopsies) and was usually scored as mild in 13 out of 21 biopsies with glomerular sclerosis and as moderate in 8 biopsies. In the triple therapy group, the global glomerular sclerosis in all grafts was always scored as mild. Capillary changes were infrequent and there was no inflammation in the glomeruli.

Vessels. There was a sufficient number of vessels in 96% of all biopsies, and 54% of all biopsies had normal blood vessel structure. Only two salient vascular changes could be identified with vessels. One of these was intimal proliferation (39% of biopsies) and the second feature consisted of vascular arteriosclerosis (24% of biopsies). These changes were seen most often in patients receiving CyA plus MP therapy (intimal proliferation in 55% and arteriosclerosis in 35% of biopsies) but seldom in those receiving triple therapy (23% and 8%, respectively). Intimal proliferation was mostly seen in arterioles but also in medium-sized arteries, and allograft arteriosclerosis was also seen in arterioles. Inflammation in vessel wall (arteritis, vasculitis) was rather uncommon and was present in only 4% of all biopsies, none in the triple therapy group. Intimal proliferation was related to tubular atrophy and to mesangial matrix increase in glomeruli.

Tubuli. Isometric vacuolation in proximal tubules was seen in all CyA treatment groups (16% of all biopsies) but in no single biopsy in the Aza plus MP group. Anisometric vacuolation was similar in every group (mean 56% of biopsies). The intensity of vacuolation was mild.

Epithelial swelling was seen in 43% and tubular atrophy in 67% of all biopsies; in the triple therapy group the frequencies were 23% and 54%, respectively. Intensity of atrophy was scored mostly as mild in the triple therapy group and as moderate in half of the biopsies in the other treatment groups. No tubulitis was found.

Basement membrane thickening was more common in the groups using CyA (18%–45%) than in the Aza plus MP group (10%). Basement membrane thickening was most intensive in the CyA plus MP group.

Correlation of histology to graft function

The interrelationships seen between morphological changes and serum creatinine or donor age are shown in Table 4. The degree of diffuse interstitial fibrosis was re-

Table 4. Correlation of histological findings to serum creatinine, donor age, and cyclosporin concentration. Spearman rank correlation coefficient test used for *P* values

Histological feature	Correlation		
	Serum creatinine *P*	Age of donor *P*	CyA concentration *P*
Interstitium			
Diffuse inflammation	0.011	NS	NS
Diffuse lymphocytes	0.014	NS	NS
Diffuse pyroninophilic cells	NS	NS	0.025
Diffuse fibrosis	0.002	NS	NS
Glomeruli			
Mesangial matrix increase	0.024	NS	NS
Bowman capsular thickening	NS	0.026	NS
Glomerular sclerosis	0.028	NS	NS
Vessels			
Intimal proliferation	0.006	0.005	NS
Sclerosis	NS	NS	0.024
Tubuli			
Epithelial swelling	NS	NS	NS
Isometric vacuolation	NS	NS	0.006
Tubular atrophy	0.0001	0.0005	NS
Basement membrane thickening	0.027	0.033	0.037
Tubular dilatation	0.047	NS	0.016

Table 5. Sum of histological scores (diffuse inflammation, lymphocytes, and fibrosis in interstitium; mesangial matrix increase and global sclerosis of glomeruli; intimal proliferation of vessels and tubular atrophy, basement membrane thickening, and dilatation of tubuli) that correlated to graft function

	Triple	Aza + CyA	Aza + MP	CyA + MP	Kruskal-Wallis *P*
Sum of scores	1.6	3.8	3.9	4.9	0.048

lated to the serum creatinine level, but there was no correlation to donor age, CyA dose, or CyA concentration. Intimal proliferation of the vessels was correlated to serum creatinine level but also to donor age. There was a significant correlation between CyA dose and concentration to the following tubular changes: isometric vacuolation, basement membrane thickening, and tubular dilatation. Treatment for acute rejection during the first 6 months postoperatively did not correlate to any one of the histopathological features.

For a comparison of the four treatment groups, the sum of scores was calculated from those histological tubulointerstitial, vascular, and glomerular changes that correlated with graft function. The sum was lowest in the triple therapy group (Table 5).

Discussion

This report is based on a prospective, randomized clinical trial to analyze the occurrence and severity of long-term histopathological changes in renal allografts using different modes of immunosuppressive therapy. Thirty-four different histological variables were scored in 54 separate protocol biopsies. Changes seen were usually present only in some of the evaluated parameters, and mostly the changes were scored as mild. The differences between the four groups were marginal, although the changes in the triple therapy group were most often less prominent than those in any one of the double drug regimen groups.

The main histological features ascribed previously to chronic rejection are perivascular and interstitial inflammation, fibrosis, glomerular sclerosis, and vascular intimal hyperplasia and tubular atrophy [17]. The glomerular and tubular changes are interpreted as being due to vascular alterations in grafts, leading to glomerular and tubulointerstitial ischemia. In this clinical trial, interstitial fibrosis, glomerular, vascular, and most of the tubular changes were found to be less frequent in the triple therapy group. Still, mild changes were seen in every group, indicating slight renal damage, even in grafts with good function. The sum of scores consisting of those histological changes correlating to graft function was lowest in the triple therapy group, indicating that allograft damage was the least in the triple therapy group.

The main concern when using CyA is the potentially progressive and irreversible nephropathy [13, 14]. Several histopathological studies have attempted to define the diagnostic characteristics of chronic CyA nephrotoxicity [9, 11, 15]. The renal histopathological changes that have previously been ascribed to cyclosporin include proximal tubular vacuolation, interstitial fibrosis, tubular atrophy, and arteriolopathy [11, 19, 21]. Most of these reports have excluded allografts with stable graft function. When no rejection pattern was evident during periods of renal dysfunction, the unusual histological features were considered as being associated with CyA [18]. Comparisons to stable grafts under Aza were rarely made. In our study, almost all patients had stable graft function, and the biopsies were taken from all grafts according to protocol. The patients in one of the groups received no CyA, only Aza and MP. In these patients having relatively stable graft function, we failed to demonstrate any specific light-microscopic, long-term histopathological features related to CyA nephrotoxicity other than isometric vacuolation. In other words, in our study, isometric vacuolation in proximal tubules was seen only in CyA groups. Other tubular changes, such as basement membrane thickening, were also more frequent in groups using CyA than in the Aza plus MP group.

Fibrosis and tubular atrophy are presumed to be dose-dependent on CyA, and low maintenance doses of CyA do not contribute to the renal damage [9]. Tubular isometric vacuolation has been reported to disappear after conversion to Aza [22]. No differences in fibrosis at 1 year were shown between the Aza plus MP group and the CyA group converting early to Aza [12]. The findings in our study are in accordance with these results. In our study, all groups receiving CyA initially had low-dose CyA, and fibrosis was scored as mild in every group. Fibrosis was also present in the Aza plus MP group. Diffuse fibrosis was strongly correlated to serum creatinine but not to CyA concentration. Interstitial fibrosis may be the effect both of chronic rejection and of CyA nephrotoxicity.

The most frequent abnormality in vessels was intimal proliferation, both in arterioles and in medium-sized arteries. Arteriolopathy is reported to be caused by CyA [1, 2, 15]. In our study, intimal proliferation was seen most often in the CyA plus MP group, and the intensity was also the highest in the CyA plus MP group, but there were no differences between the two other groups using CyA and the Aza plus MP group. All vascular changes were less frequent in the triple therapy group.

Recently, a study showed that in long-term patients, the maintaining of higher CyA levels achieved better graft function without evidence of chronic CyA toxicity, suggesting that rejection due to inadequate immunosuppression is a greater risk than nephrotoxicity [16]. Both fibrosis and vascular changes are reported to be caused by CyA or chronic rejection [4, 6]. In this study, diffuse fibrosis and intimal proliferation were correlated with graft function. Diffuse fibrosis and intimal proliferation and vascular sclerosis were seen more often in the CyA plus MP group than in the other groups, and there was a significant difference in diffuse fibrosis between the triple therapy and CyA plus MP group, which might be the effect of both CyA toxicity and better immunosuppression with triple therapy.

Retrospective studies have suggested that acute episodes of rejection contribute to the development of chronic rejection [3]. We did not find any correlation be-

tween previous acute rejection episodes and histopathological changes in grafts at 2 years. However, the frequency of acute rejection was low in this trial (0.2 rejection per patient during the first month).

Core biopsies of renal allografts were evaluated for specific CyA changes and to determine whether there were any differences in chronic renal damage between the four groups 2 years after transplantation. Our results demonstrate that the only CyA-specific parameter was isometric vacuolation in proximal tubules. Chronic allograft damage (tubulointerstitial, glomerular, and vascular changes) was seen less frequently in the triple therapy group. However, biopsy findings showed mild changes in every treatment group 2 years after renal transplantation.

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