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Histopathology of Human Renal Allograft Rejection under FK 506: A Comparison With Cyclosporine

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FK 506, a powerful new immunosuppressant, was first used in humans in an attempt to salvage liver and kidney allografts that were failing because of rejection.[1] Thereafter, allograft recipients who were experiencing disabling side effects of standard cyclosporine (CyA) and steroid baseline therapy were switched to FK 506 as well.[1] The relative safety of the drug then permitted trials of FK 506 as the initial immunosuppressant as maintenance therapy for primary liver allograft recipients.[2] Bolstered by the success with liver allografts, FK 506 was tested as primary therapy in recipients of new kidney allografts.[3]

In our initial report, we detailed the pathologic findings in the earliest recipients of FK 506, most of whom had received liver allografts.[4] Comparison of the incidence and histologic features of acute cellular rejection in this group to historic controls maintained on CyA revealed some distinct differences. First, the incidence of acute cellular rejection was less in those treated with FK 506 than in the historic CyA treated controls.[4] Second, although the histologic appearance of liver allograft rejection in patients treated with FK 506 was similar to that seen under CyA and steroids,[4] central venulitis as part of rejection was more prominent in the former. This report focuses on the histopathology of renal allograft rejection in comparison to contemporaneous CyA/steroid treated controls.

Since the initial renal allograft recipients treated with FK 506 were "high risk," they were not randomly assigned to treatment groups.[3] Also, the renal biopsies in this series of patients were performed because of dissatisfaction with the clinical course or uncertainty about the diagnosis. It should be noted that pathology specimens were obtained more often in the CyA treated patients. Therefore, a distinct comparison of the incidence or severity of rejection was not considered valid. We had, however, more simple goals in mind for this initial study. They were (1) to determine if histologic features observed in renal allograft biopsies during episodes of clinically suspected rejection differ in patients with FK 506 compared with those treated with CyA as the baseline immunosuppressant; (2) to determine if histologic features associated with clinical rejection correlate with renal dysfunction as measured by serum creatinine levels; and (3) to determine if classic prognostic features of rejection are valid under this new immunosuppressive agent.

PATIENTS AND METHODS

The patients were selected for this study on the basis that they received a renal allograft in the 6-month period between June and December 1989. Furthermore, each of the patients experienced graft dysfunction within the first 3 posttransplant months for which a needle biopsy was performed. The patients chosen included 26 who were treated with CyA and 19 immunosuppressed with FK 506 as the baseline drug. Both groups (CyA and FK 506) of patients were initially given steroids, although the doses were rapidly tapered in the FK 506 groups.[3] Therefore, maintenance steroid therapy was, on the average, much lower in the FK 506 treated group. General patient data, the number and type of pathology specimens, and the immunologic status prior to transplantation are shown in Table 1. There was no difference in the type or incidence of native renal diseases between the two groups (data not shown).

Table 1. Patient and Pathologic Data and Immunologic Profile Prior to Transplant

	CyA	FK 506
Patients	26	19
Male:female	17/9	11/8
Average age (range)	41(16-72)	42(18-67)
Biopsies	70	36
Failed allografts	7	3
Prior kidney transplant	4(15%)	5(26%)
Pediatric en bloc	6(25%)	2(11%)
Living related donor	2(8%)	0
PRA >20%*	4(16%)	6(32%)
Equivalent or positive crossmatch†	9(36%)	7(37%)
Average antigen matches (range)	1.9(0-6)	1.5(0-3)

Note. None of the differences are statistically significant (chi-square analysis) except for the use of living related donors in the CyA group.
Abbreviations: PRA, panel reactive body.
*Based on current or historic (less than 6 months) sera.
†Equivocally or frankly positive crossmatch after treatment with dithiothreitol (DTT).

Table 2. Histologic Features Assessed in the Coded Review of Slides

Structure	Feature Assessed
Glomerulus	Average number, cellularity, capillary loop integrity and thrombosis, and crescents
Tubular epithelium	Vacuolization, necrosis sloughing, inflammation
Interstitium	Edema, fibrosis (severity), inflammation (severity and type), hemorrhage necrosis
Arteriole/arteries	Thrombosis, fibrinoid necrosis, inflammatory arteritis, arteriolar thickening

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Table 3. Incidence of Histopathologic Changes Observed in the Allograft Biopsies and Failed Allografts

	CyA	FK 506
Glomeruli		
Average number*	9	15
Cellularity		
Normal	51	28
Increased	22 (30%)	10 (26%)
Thrombi†	19 (25%)	4 (11%)
Crescents	1	1

*In biopsies only.
†Most were seen in biopsies taken during the first posttransplant week and most likely represent preservation related changes.

All biopsies were performed upon clinical indication. Coded biopsy slides were reviewed in sequence, separately by the two pathologists. They had no knowledge of the type or changes in immunosuppressive therapy. The presence or absence, and where appropriate, the degree of histologic changes were scored for each biopsy. The histologic features assessed are shown in Table 2. A diagnosis was then rendered and the results compared. Conventional histopathologic criteria were used as the basis for the diagnosis of acute cellular and humoral rejection. Thereafter, any result showing disagreement between the pathologists for a particular feature was re-reviewed and a consensus was made. Thereafter, the treatment code was broken.

RESULTS

Histopathologic Changes

The changes observed in the glomeruli are listed in Table 3. There was no statistically significant difference in the findings between the two groups. The thrombi seen in the glomeruli were most commonly observed in the first posttransplant week and likely related to preservation. Drug treatment may also be contributory.

Tubular epithelial changes were most commonly seen in the proximal convoluted portion. These are summarized in Table 4. No statistically significant differences were seen between the two groups.

The interstitial changes are summarized in Table 5. Again, there was no statistically significant difference between the two groups. The composition of the infiltrate was also evaluated by light microscopy and no significant differences was noted.

The histologic changes observed in the arterial tree are summarized in Table 6. Again, no statistically significant difference was noted between the two groups. The presence of fibrinoid necrosis was accompanied by immune deposits and/or interstitial inflammation in both groups.

Table 4. Summary of the Incidence of Proximal Tubular Epithelial Changes

	CyA (%)	FK 506 (%)
Normal	7 (9)	5 (13)
Vacuolated	29 (38)	12 (31)
Necrosis/sloughing*	10 (13)	4 (10)

*Most of these were accompanied by regenerative changes as well.

Table 5. Summary of the Incidence of Histopathologic Interstitial Changes

	CyA (%)	FK 506 (%)
Edema	19 (26)	9 (23)
Fibrosis		
None	40 (52)	19 (49)
Mild	28 (36)	14 (36)
Moderate	5 (6)	6 (15)
Severe	0	0
Inflammation		
None	17 (22)	8 (21)
Mild	39 (51)	21 (54)
Moderate	18 (23)	7 (18)
Severe	2 (3)	2 (5)
Hemorrhage	16 (22)	4 (11)

This indicates the necrosis observed was likely a consequence of rejection.

Histopathologic Diagnosis and Clinicopathologic Correlation

A summary of the incidence of the histopathologic diagnosis of rejection is shown in Table 7. As can be seen, there was no statistically significant difference between the two groups. The clinicopathologic correlation for the patients treated with FK 506 is shown in Table 8. Rejection (cellular and humoral) was treated by an increase in FK 506, steroids, or OKT3. As can be seen, treatment of changes typically associated with acute cellular rejection resulted in an improvement in renal function as assessed by serum creatinine. No response, however, was observed in patients with humoral rejection.

Finally, classic prognostic features associated with a poor prognosis in rejection were analyzed in both groups. The presence of arterial fibrinoid necrosis and intestinal hemorrhage in either group presuaged graft failure in most instances. For patients treated with FK 506, three of the four patients who had intestinal hemorrhage in biopsy specimens lost their graft in the first 3 months ($P < .05$ chi-square analysis).

DISCUSSION

This pilot study demonstrates that conventional histopathologic criteria for the diagnosis of acute cellular and humoral rejection of renal allografts can be applied to biopsies from human kidney graft recipients treated with FK 506. Although there was a trend toward a lower

Table 6. Summary of the Incidence of Changes in the Arterial Tree

	CyA (%)	FK 506 (%)
Thrombosis	9 (12)	4 (11)
Fibrinoid necrosis	10 (14)	2 (6)
Inflammatory arteritis	24 (32)	7 (19)
Arteriolar thickening	24 (33)	17 (46)

Table 7. Incidence of the Histopathologic Diagnosis of Rejection

	CyA (%)	FK 506 (%)
Predominantly humoral rejection	3 (4)	3 (8)
Predominantly cellular rejection	54 (70)	23 (60)
Other	20 (26)	13 (32)

incidence of findings associated with more severe rejection in patients treated with FK 506, the differences were not statistically significant in this small population. Furthermore, the number of biopsies in CyA treated patients was greater. Some of the features commonly associated with CyA nephrotoxicity (proximal tubular vacuolization and glomular thrombosis) were also observed in biopsies from patients treated with FK 506. The effect, if any, of FK 506 or renal structural integrity will require long-term follow-up studies. Finally, a more direct comparison of the two drugs will have to be assessed in a randomized trial, currently underway.

Table 8. Clinicopathologic Correlation Between the Biopsy Diagnosis, Change in Immunosuppressive Therapy, and Effect on Renal Function in Patient Treated With FK 506

Pathology Diagnosis	No. of Patients	Alteration in IS Therapy	Change in Serum Creatinine
ACR	7	Increased	Decreased
ACR	1	No change	Decreased
Predominantly humoral	3	Increased	Increased
Other	3	Decreased	Decreased
Other	4	No change	Decreased or same

Abbreviations: IS, immunosuppressive therapy; ACR, acute cellular rejection.

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