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Late histopathological findings in renal allografts with four immunosuppressive regimens*

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The histological changes in renal allografts are usually studied when graft function has already deteriorated. The early results of renal allografts have improved dramatically during the last two decades, but the half-life of renal cadaveric allografts has remained unchanged at approximately 7 years [1]. The mechanism of chronic rejection, and how to prevent it, is not known. We studied the histology of renal allografts under four different immunosuppressive regimens 2 years after transplantation. The aim of this study was to investigate whether histopathological changes exist in the renal allografts with relatively good and stable graft function. We also investigated whether there were differences in allograft histology between four immunosuppressive treatment groups 2 years after transplantation.

Key words: Renal transplantation – Immunosuppression – Histopathology

Patients and methods

Originally 128 consecutive patients with a first cadaveric graft entered a prospective randomized trial. Two-year graft survival was 80% (102 patients). At 2 years all patients with a functioning graft were biopsied. This study group consisted of 89 patients who had an adequate biopsy out of the group of 102 patients. A representative biopsy of 13 grafts was not available because of contraindications to biopsy, patient refusal or inadequate biopsy.

Originally the patients were randomly allocated to four different immunosuppressive groups. One group received triple-drug therapy consisting of cyclosporine (CyA), azathioprine (Aza) and methylprednisolone (MP). Three other groups received all possible combinations of the three immunosuppressive drugs, i.e. CyA + Aza, Aza + MP and CyA + MP [2]. The initial dose of CyA was 10 mg/kg per day, at 1 year the dose was 4 mg/kg per day and at 2 years the mean dose was 3.2 mg/kg per day.

At 2 years 69/89 (78%) patients had normal or near-normal serum creatinine (< 200 µmol/l): mean 148 µmol/l, median 120 µmol/l. Mean and median serum urea were 9.8 mmol/l and 8.0 mmol/l, respectively.

All biopsies were taken two years after transplantation. An automated punch device (Biopty-Cut, Radiplast Bromma, Sweden) was used with ultrasound guidance for percutaneous needle core biopsy. Transplant specimens were obtained with an 18G needle (outer diameter 1.2 mm) which yielded biopsies of 0.9 × 20 mm. There were no biopsy-related complications using this technique except microscopic haematuria in some cases. Five different stainings were used for light microscopic examination. The specimens were coded and examined by two independent observers. The biopsy was considered representative if it contained at least five glomeruli. Every biopsy was scored separately for histopathological changes in the interstitium (focal and diffuse), glomeruli, vessels (arterioles, arteries and veins) and tubuli (proximal and distal). Altogether 34 different parameters were scored [3]. The histopathological changes were scored semiquantitatively from 0–3 (0 = no change, 1 = mild, 2 = moderate, 3 = severe change).

For testing the correlation between graft function and histological findings the Spearman's rank correlation test was used. For absolute numbers of the four groups, a contigency table was used. For the differences in the intensity of histological changes between the four treatment groups, the Kruskall-Wallis nonparametric test was used. P values > 0.05 were considered significant.

Results

Most of the 34 histological parameters examined showed no changes. Any changes that did occur were usually mild; severe changes were seldom seen. The following score changes were found: diffuse interstitial fibrosis (in 6% of biopsied grafts) diffuse interstitial inflammation (in 2%), glomerular sclerosis (in 3%) and tubular atrophy (in 2%). Diffuse interstitial fibrosis and tubular atrophy were the most common findings, in 2/3 of the grafts, but mostly scored as mild. The other histopathological changes were: diffuse inflammation in interstitium (in 30% of grafts); mesangial matrix increase (37%) and sclerosis (43%) in glomeruli; intimal proliferation (36%) and sclerosis (27%) in vessels; epithelial swelling (36%); basement

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membrane thickening (25%); anisometric vacuolation (50%); isometric vacuolation (12%); and tubular dilatation (15%). The differences in the frequency of histopathological changes between the four immunosuppressive groups were marginal. The only significant differences in the frequency of changes were in mesangial matrix increase of glomeruli ($P = 0.01$) and in vascular sclerosis ($P = 0.03$), with less frequent changes in the triple therapy group.

Decreased graft function correlated with six histological parameters. These were increasing diffuse fibrosis ($r = 0.40, P = 0.0002$) and diffuse inflammation in interstitium ($r = 0.30, P = 0.005$), sclerosis ($r = 0.33, P = 0.002$) and mesangial matrix increase ($r = 0.34, P = 0.002$) in glomeruli, intimal proliferation in vessels ($r = 0.21, P = 0.05$) and atrophy in tubuli ($r = 0.48, P = 0.0001$).

The histopathological changes were mostly of equal intensity in the four immunosuppressive groups. The only significant differences were seen in diffuse fibrosis in interstitium ($P = 0.05$), mesangial matrix increase in glomeruli ($P = 0.02$), intimal proliferation ($P = 0.03$) and sclerosis ($P = 0.03$) in vessels with fewer changes in the triple-therapy group than in the double-drug regimens. However, other histopathological changes such as diffuse inflammation, glomerular sclerosis and tubular atrophy, were less prominent in the triple-therapy group than in others although the difference was not significant.

A chronic allograft damage index was created for comparison of the four immunosuppressive treatment groups. The index consisted of those six histological parameters which correlated with decreasing graft function. These parameters were diffuse inflammation and fibrosis in interstitium, mesangial matrix increase and sclerosis in glomeruli, intimal proliferation in vessels and atrophy in tubuli. The index was significantly lower in the triple therapy group ($P = 0.009$) (Table 1).

Table 1. Chronic allograft damage index[a] in the four immunosuppressive groups. Histological biopsy was performed two years after transplantation

Triple ($n = 19$)	Aza + CyA ($n = 23$)	Aza + MP ($n = 25$)	CyA + MP ($n = 22$)	P (Kruskal-Wallis)
1.5	3.2	3.2	4.3	0.009

[a] Sum of diffuse inflammation and fibrosis in interstitium, mesangial matrix increase and sclerosis in glomeruli, intimal proliferation in vessels and tubular atrophy
Mean score per patient per group is presented

Discussion and conclusion

Two years after transplantation most of the patients (78%) had normal or only slightly increased serum creatinine. Our results demonstrate that even renal allografts with a good and stable graft function exhibit mild histopathological changes, similar to those changes seen in chronic rejection.

Most of the histopathological changes were distributed similarly in the four immunosuppressive groups. There were significant differences only in diffuse interstitial fibrosis, mesangial matrix increase, and vascular intimal proliferation with fewer changes in the triple-therapy group than in any group receiving double-drug treatment. However, there was a tendency to less-prominent histopathological changes in the triple-therapy group than in any group receiving a double-drug regimen, and to quantitate this tendency more precisely a new parameter, the chronic allograft damage index was created. The index consisted of those six parameters which were shown to correlate with decreasing graft function, i.e. diffuse interstitial inflammation and fibrosis, glomerular sclerosis and mesangial matrix increase, vascular intimal proliferation and tubuluar atrophy. These are the same histological features which have previously been reported to be associated with chronic rejection [4], which is clinically defined as a gradual but progressive decline in graft function. The chronic allograft damage index was significantly lower in the group receiving triple therapy than in the double-drug treatment groups, thus indicating fewer histopathological changes in the triple-therapy group. The changes in the Aza + MP group, were at the same level as in the other two groups receiving a double-drug regimen. We conclude that triple therapy is more efficacious than any one of the double drug regimens in the prevention of chronic histological changes in renal allografts.

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