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The increasing importance of chronic rejection as a cause of renal allograft failure

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Abstract. A consequence of reducing early graft failure due to acute rejection has been that more patients are at risk of chronic rejection, something which has become an increasingly important cause of graft loss. We examine the graft survival rates and reasons for failure in our unit from 1981 to 1986. Patients were divided into two series according to treatment of acute rejection episodes. From 1983 onwards, by treating acute vascular (poor prognosis) episodes with antilymphocyte globulin (ALG), we have significantly improved the 6-month actuarial graft survival rate. However, the percentage of total graft failure due to chronic rejection in this second series has significantly increased. The need for greater understanding of the aetiology of chronic rejection, together with its present unsatisfactory treatment, is discussed.

Key words: Renal transplantation, chronic rejection - Chronic rejection, in renal transplantation.

We have previously reported the poor prognosis for renal transplants that suffer episodes of acute vascular rejection [26], and since 1983 we have treated such episodes aggressively with antilymphocyte globulin (ALG) or by conversion from azathioprine to cyclosporin.

ALG was first used as an immunosuppressive agent in renal allograft recipients over 20 years ago [21], but trials have not shown benefit from its prophylactic administration [1, 22, 25]. However, a significant increase in graft survival rate is achieved in patients given ALG (usually in addition to steroid therapy) as treatment for rejection episodes when compared to controls receiving steroids alone [6, 11, 12]. This finding has been confirmed in our experience, with an encouraging improvement in early results [7].

A consequence of reducing early graft loss has been that more patients are at risk from the long-term complications of transplantation, notably chronic rejection. This paper examines the changing pattern of graft failure in our unit, with a minimum patient follow-up of 3 years (up to April 1989).

Patients and methods

Between January 1981 and June 1986, 154 transplants were performed using low-dose prednisolone and azathioprine immunosuppression prescribed according to the "Belfast Regimen" [17]. Trucut needle biopsies were performed in all cases of graft dysfunction if rejection was suspected and at least every 7 days if the onset of graft function was delayed. Poor prognostic (vascular) rejection was diagnosed on the following histological criteria [10]:

1. Arterial wall necrosis (grade 1)
2. Glomerular necrosis (grade 2)
3. Both mononuclear cell adherence to vessel walls and interstitial haemorrhage (grade 2)

In 1981 and 1982 (series I), all rejection episodes were treated with a reducing course of high-dose oral steroids according to the following protocol: 200 mg for 3 days, 150 mg for 3 days, 100 mg for 3 days, 50 mg for 3 days. After January 1983 (series II), patients with vascular rejection received oral steroids as above and either intravenous ALG (Pressimmune, Hoechst, 30 mg/kg daily for 7 days) or, in the latter part of the series, conversion to cyclosporin. Patients in whom biopsy showed rejection without vascular features were treated with oral steroids alone.

Patient characteristics

Series I included 50 patients (34 male, 16 female) with a mean age of 35 years (SD 12 years). Among them were 9 patients with second transplants and 1 with a living related transplant. Series II included 104 patients (65 male, 39 female) with a mean age of 32 years (SD 12 years). Among these patients were 15 with second/third transplants and 2 with living related transplants.

All patients were followed up for a minimum of 3 years. Causes of graft failure were determined using available clinical

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and pathological information. In patients whose grafts had failed, a diagnosis of chronic rejection was only made when the following conditions were met:

1. The graft failed at least 6 months after transplant.
2. The time period of deterioration of graft function, as determined by the graph of reciprocal of plasma creatinine against time, was at least 3 months.
3. Histological examination of a graft biopsy prior to the withdrawal of immunosuppression revealed the typical obliterative vascular features with intimal proliferation [19].
4. There was no clinical or histological evidence for another cause of graft failure.

In patients with graft function remaining, a diagnosis of chronic rejection was only made when the following conditions were met:

1. They were at least 6 months after transplant.
2. The regression of the graph of reciprocal of plasma creatinine against time was significantly different from zero.
3. Histological examination of a graft biopsy demonstrated the characteristic changes of chronic rejection.
4. There was no clinical or histological evidence for another cause of graft dysfunction.

Life table analysis was performed using the method employed by Peto et al. [18]. Patient death with a functioning graft was counted as graft loss.

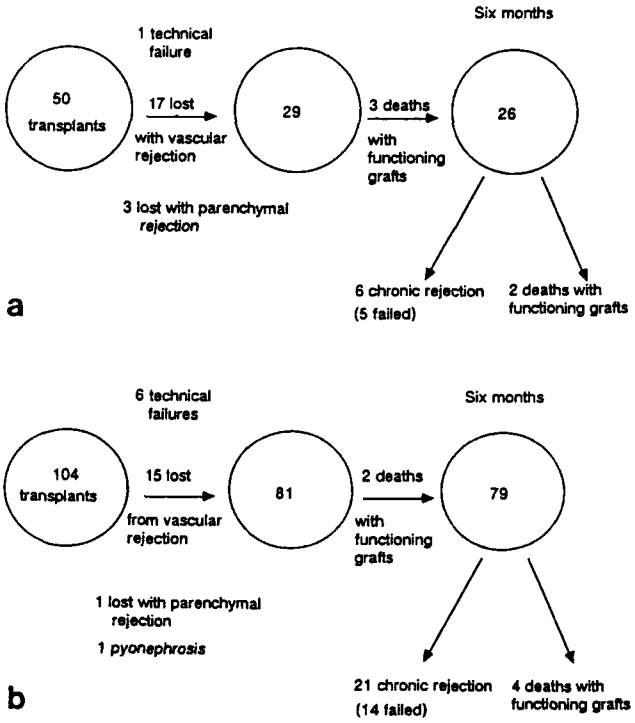

Fig. 1. Flow chart of results. a Series I; b series II

Results

The results of the two series are summarised in Table 1 and Fig. 1.

Series I: 1981-1982 (50 transplants)

One graft was lost for technical reasons in the first 24 h and was, therefore, not at risk of acute rejection. Of those that remained, 21 (43%) had one or more episodes of vascular rejection, which in 17 cases (35%) resulted in graft loss. Twenty-four (49%) had one or more episodes of rejection without any vascular features, and 3 (6%) of these lost their grafts. Four patients had no rejection. Three patients died in the first 6 months with grafts still functioning. Twenty-six transplants (52%) survived to 6 months. From 6 months onwards, 6 patients subsequently developed chronic rejection. Five have already lost their grafts; 1 has some function remaining. Of these 6 grafts with chronic rejection, 1 had survived an early acute vascular rejection and 5 had experienced acute rejection episodes without vascular features.

From 6 months onwards, 2 patients subsequently died with functioning grafts and 1 patient has developed recurrent primary renal disease in his graft.

Table 1. Summary of results

Series I	Failed <6 months	Failed from chronic rejection	Functioning with chronic rejection	Died with function		Stable grafts
				<6 months	>6 months	
Acute vascular rejection	17	1	0	1	0	2
Acute parenchymal rejection	3	4	1	1	1	13
No acute rejection	0	0	0	1	1	2
Series II						
Acute vascular rejection	15	9	3	1	2	13
Acute parenchymal rejection	1	5	4	0	1	39
No acute rejection	0	0	0	1	1	2

Series II: 1983-1986 (104 transplants)

Six grafts were lost due to technical problems in the first 24 h. Of the remaining 98 grafts, 45 (43%) had at least one episode of vascular rejection; 39 of these were treated with ALG and 6 by conversion to cyclosporin. In 15 cases (33%), treatment was unsuccessful, and graft failure within 6 months resulted. Forty-six grafts (44%) had one or more episodes of rejection without any vascular features, and only

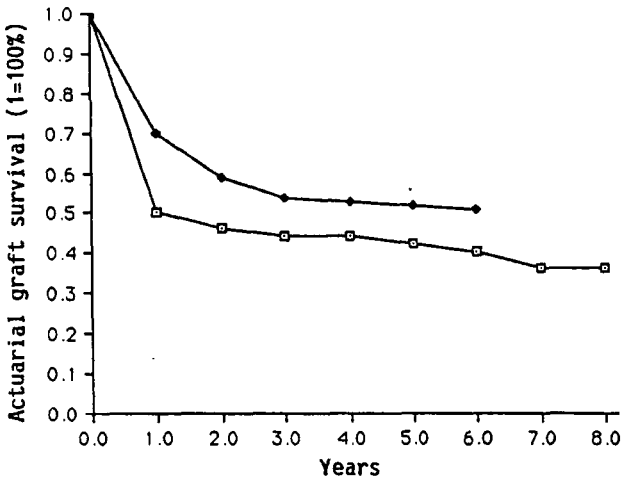

Fig. 2. Actuarial graft survival. ⊡, Series I; ◆, Series II

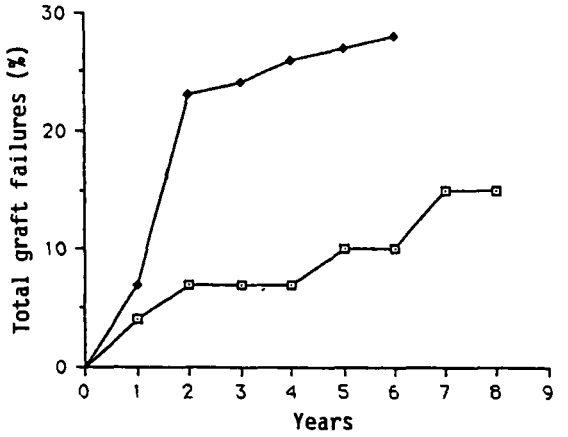

Fig. 3. Percentage of total graft failures due to chronic rejection in each series. Symbols as for Fig. 2

1 patient (2%) lost his graft. Seven patients had no rejection. Two patients died with functioning grafts in the first 6 months. One patient developed a pyonephrosis after 2 months and subsequently lost her graft. Seventy-nine transplants (76%) survived to 6 months.

From 6 months onwards, 21 patients developed chronic rejection, 14 of whom have already lost their grafts; the other 7 have some function. Twelve from this group had survived a vascular rejection, and 9 had experienced acute rejection without vascular features. As in series I, all grafts developing chronic rejection had suffered previous episodes of acute rejection. Four patients died with functioning grafts more than 6 months after their transplants.

The actuarial graft survival rates of both series are shown in Fig. 2. The 6-month actuarial graft survival rate in series II (76%) is significantly better than that in series I (52%; Chi^2 8.937; $P<0.01$). After 3 years the difference is no longer significant (Chi^2 2.224; $P<0.1$).

Figure 3 shows the percentage of graft losses in each series caused by chronic rejection. Clearly in the immediate post-transplant period, most graft losses were due to acute rejection, but after 3 years chronic rejection had accounted for significantly more losses in series II (24%) than in series I (7%; $P=0.048$; Fischer's exact test).

Discussion

The incidence of acute vascular rejection was similar in the two series, but aggressive treatment in the second group resulted in a significant improvement in the 6-month actuarial graft survival rate. The greater number of grafts therefore at risk from 6 months onwards resulted in a higher incidence of chronic rejection in series II. Furthermore, we have already found that chronic rejection is more likely to occur in patients who have acute vascular rejection than in those who do not. This has also been our finding in a multivariate analysis of the risk factors for chronic rejection [8].

Our series mainly concern patients receiving azathioprine and prednisolone, but chronic rejection and late graft loss also remain a problem in patients whose initial immunosuppression is with cyclosporin. Similar rates of graft attrition are reported in randomised trials comparing these two treatment groups [2-4]. Our findings have confirmed that chronic rejection is the major cause of late graft loss, but treatment remains unsatisfactory, partly due to its uncertain aetiology [5]. The characteristic vascular obliteration that occurs is considered to be a result of platelet deposition on endothelium that has been previously damaged by an antibody-mediated reaction [24]. This has led to trials of anticoagulants, antiplatelet drugs [13], and prostaglandins [15, 23]. Dipyridamole, given prophylactically with anticoagulants, has been shown to reduce the severity of intimal lesions seen in the immediate post-transplant period, although this treatment produced no difference in graft survival after a mean patient follow-up of 2.5 years [13, 16]. Plasma exchange [9] and pulses of steroids [14] have been tried, and in our own unit the conversion of patients on azathioprine to cyclosporin has resulted in some useful delay in the return to dialysis [20], but as yet graft loss appears inevitable. This defeats the ultimate aim of transplantation, which is to achieve permanent graft acceptance, and thus chronic rejection and late graft loss demand further study.

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