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Long-term effects of steroid withdrawal in kidney transplantation

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Abstract. The long-term graft function after withdrawal of steroids from maintenance immunosuppression was analyzed in 98 kidney recipients (59 on cyclosporin monotherapy, 39 on cyclosporin plus azathioprine) who had not developed an early rejection episode when prednisolone was discontinued. Seven years after steroid withdrawal the probability of an increase in serum creatinine (> 20% of baseline levels) was 51%. The increase in creatinine was associated with sclerosing arteriopathy as a marker of chronic rejection in 29 of 43 graft biopsies. The addition of azathioprine had no effect on the stability of long-term graft function and did not influence the 7-year graft survival rate in this highly selected group of patients.

Key words: Steroid withdrawal, kidney transplantation – Kidney transplantation, steroid withdrawal – Conversion, steroid to azathioprine, kidney transplantation

Introduction

In 1989 we reported in this journal [7] on the probability of developing acute rejection episodes after steroid withdrawal in kidney graft recipients initially treated with cyclosporin plus prednisolone. During the 1st year without steroids, the risk of rejection was 48% with cyclosporin monotherapy and 28% with cyclosporin plus azathioprine ($P < 0.05$). The 141 patients included in this study were transplanted between December 1982 and November 1986. We have now reinvestigated the long-term outcome in these patients to assess the effect of azathioprine beyond the 1st year, the risk of developing chronic rejection, and the probability of late graft failure.

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Patients and methods

Details of the original study design, patient data, and histological findings in graft biopsies have previously been reported [7]. Steroid medication was withdrawn in 141 out of 256 consecutively transplanted patients 7–9 months after kidney transplantation. After steroid withdrawal immunosuppression was continued with cyclosporin monotherapy in 88 patients and with cyclosporin plus 50 mg azathioprine per day in 53 recipients. During the first 4 months after steroid withdrawal, 43 patients (29 on cyclosporin monotherapy and 14 on cyclosporin plus azathioprine) developed acute rejection episodes confirmed by graft biopsy and were returned to steroids.

To assess the late effects of steroid withdrawal and of additional azathioprine medication, the events, creatinine increase or graft failure, in the 98 remaining recipients who were still free of steroids 1 year after transplantation were evaluated. Fifty-nine of these 98 patients were on cyclosporin monotherapy and 39 received cyclosporin plus azathioprine.

The patients were returned to steroids when the serum creatinine increased rapidly or gradually by more than 20% of their baseline levels. A graft biopsy was performed at this time in all cases, except in patients who refused the biopsy ($n = 4$) or in whom the elevated creatinine was very rapidly reversible ($n = 5$).

Chronic rejection was defined as sclerosing arteriopathy [1, 4] in the graft histology. This finding was often combined with diffuse interstitial fibrosis, with or without glomerulopathy.

The probability of remaining free of steroids and the graft survival rates were calculated using the Kaplan-Meier estimate [5] and compared with the log-rank test.

Results

For the original group of 141 patients who had entered the study, the probability of being free of steroids 7 years after steroid withdrawal was 30% (20% on cyclosporin monotherapy and 42% on cyclosporin plus azathioprine). In absolute numbers 46 of the original 141 patients were still off steroid medication at the end of observation: 20 on cyclosporin monotherapy and 26 on cyclosporin plus azathioprine.

For the 98 patients who received no steroids 1 year after transplantation (3–5 months after steroid withdrawal), the probability of still being without steroids 7 years after steroid withdrawal was 49%. In this late

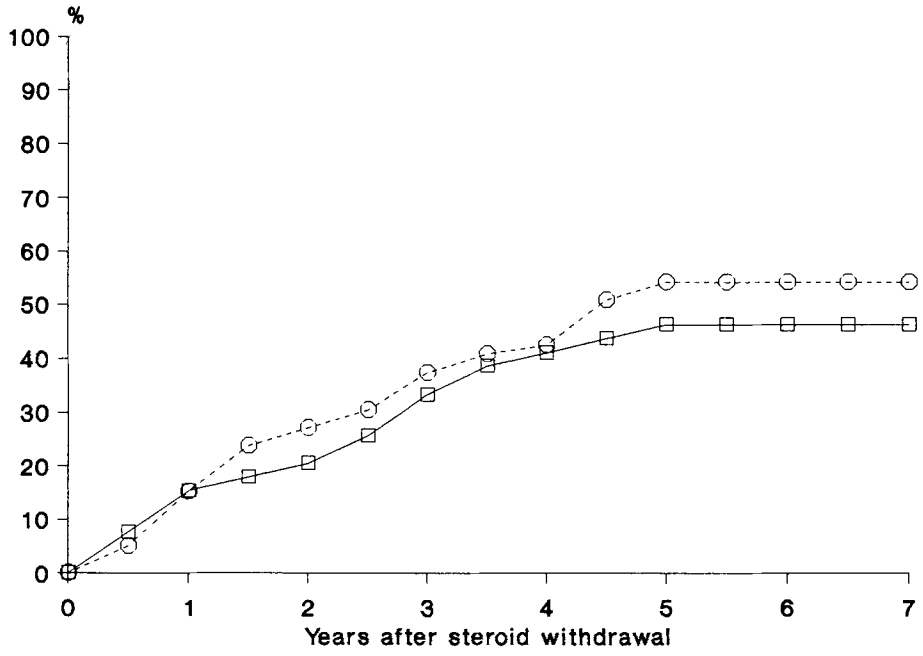

Fig. 1. Probability of being returned to steroids for 98 kidney graft recipients on maintenance immunosuppression without prednisolone 1 year after transplantation. Fifty-nine of the patients were on cyclosporin monotherapy (-O-) and 39 were on cyclosporin plus azathioprine (-□-). $P > 0.1$ (NS)

Table 1. Histological findings in graft biopsies and development of graft function (serum creatinine) in 43 kidney recipients returned to steroid medication

Graft biopsy findings (Mean time after transplantation	*n*	Short-term steroid effect on creatinine	*n*	Long-term creatinine levels	*n*
Interstitial infiltrate (22.7 ± 11.5 months)	7	Complete remission	7	Stable	7
Interstitial infiltrate plus sclerosing arteriopathy (33.6 ± 18.7 months)	8	Complete remission Partial remission No effect	3 2 3	Stable Slowly rising Dialysis	3 5 1
Sclerosing arteriopathy plus fibrosis or glomerulopahty (39.9 ± 21.5 months)	21	Complete remission Partial remission No effect	8 5 8	Stable Slowly rising Dialysis	12 9 4
Normal graft histology (31.8 ± 14.2 months)	5	No effect	5	Stable Slowly rising	3 2
Cyclosporin vasculopathy (64 months)	1	–		Stable	1
HUS recurrence (40 months)	1	–		Dialysis	1

phase no significant difference ($P > 0.05$) was observed for patients on cyclosporin alone ($n = 59$) or on cyclosporin plus azathioprine ($n = 39$; Fig. 1).

The 7-year graft survival rate in these 98 patients was 77.5% ± 5.0%. There was no difference ($P > 0.1$) in the graft survival rates whether the patients received additional azathioprine (78.4% ± 9.1%) or whether they were on cyclosporin monotherapy (77.0% ± 5.5%).

For the 43 patients with acute rejection episodes during the first 4 months, the 7-year graft survival rate was 72.1% ± 7.9% and not significantly ($P > 0.1$) different from the results in the 98 patients described in this report.

Of the 52 patients returned to steroids during the observation period, 43 had a graft biopsy to diagnose the cause of the creatinine increase (Table 1). Sclerosing arteriopathy as a marker of chronic rejection was found in 29 biopsies. Additional mononuclear cell infiltrates were found in 8 of these 29 biopsies. Acute interstitial cell infiltrates were found in 7 patients, and 5 biopsies showed no signs of graft rejection. In 1 biopsy each, cyclosporin vasculopathy or recurrent hemolytic uremic syndrome (HUS) was found.

The patients received a short course of prednisolone rejection treatment and stayed on 4 mg methylprednisolone per day thereafter. A complete remission to baseline creatinine levels was achieved in the patients with acute cell infiltrates alone and in 11 of 29 recipients with histological signs of chronic rejection; 7 of these patients had a

partial remission and 11 showed no effect. Despite histological signs of chronic rejection, graft function remained stable in 15 of 29 patients; in 14 the serum creatinine increased slowly despite repeated rejection treatment, with the need for dialysis in 5 patients.

Discussion

In the early phase after steroid withdrawal, the addition of azathioprine to the cyclosporin therapy significantly reduces the risk of acute rejection episodes [6, 7]. In later stages the development of chronic rejection is obviously not influenced by additional azathioprine.

It is not known to what extent withdrawal of steroids contributes to the development of chronic rejection. In a randomized trial, the Canadian Transplant Study Group [3] observed no adverse effect on graft outcome when prednisone was discontinued in stable patients. Griffin and Salaman [2] reported similar long-term results with immunosuppressive regimens where prednisolone was not used.

In the present study the patients withdrawn from steroids had excellent long-term graft survival. The development of chronic rejection does not seem to be influenced by the regimen used for maintenance immunosuppression. Whether reinstitution of steroid medication is of any benefit in chronically rejecting patients cannot be answered from the data of this investigation. Despite histological signs of chronic rejection in the graft biopsy, half of the patients maintained a stable graft function with this policy of reinstituting steroid medication.

In conclusion, in stable kidney graft recipients, prednisolone can be discontinued without presenting any long-term risk to the graft function. In the highly selected patients reported here (no early rejection episode after steroid withdrawal), additional azathioprine had no significant effect on long-term graft stability.

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