

CYCLOSPORIN A OR AZATHIOPRINE COMBINED WITH PREDNISONE IN RENAL ALLOTRANSPLANTATION WITH CONVERSION FROM CYCLOSPORIN A TO AZATHIOPRINE AT FOUR MONTHS

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Summary

Cyclosporin A in combination with steroids is effective in both cadaver and living related allografts. However, infection, hepatotoxicity and nephrotoxicity is common. Conversion to azathioprine by overlapping a full dose of azathioprine with a gradually decreasing dose of Cyclosporin A while increasing the steroid doses temporarily is not associated with breakthrough rejection and results in significant improvement in renal function, particularly in patients with nephrotoxicity.

Introduction

Cyclosporin A has been found superior to azathioprine when either is combined with steroids, particularly among immunologically high risk cadaver recipients [1], or where graft survival in the azathioprine group is low [2,3], presumably also indicating an immunologically high-risk patient population.

Because of the high cost of Cyclosporin A, its nephrotoxicity and hepatotoxicity, as well as the uncertain effects of its long-term use, we developed a protocol for conversion to azathioprine four months after transplantation.

We report here the preliminary results of our comparative study between Cyclosporin A and azathioprine, both combined with steroids in living related allografts and Cyclosporin A combined with steroids in cadaver allografts with an elective conversion protocol at four months after transplantation.

Patients and methods

Sixty-four patients were transplanted between February, 1983 and March, 1985 and followed up for three to 27 months (median of 12 months). There were 41 males and 23 females. Their ages ranged from 14 to 60 years with a mean of 36.1 years for the Cyclosporin A group and 34.0 years for the azathioprine

group. All but one of the recipients had at least one third-party transfusion before transplantation, 44 per cent had five or more transfusions. All living related 1-DR match recipients except one had three donor specific transfusions. Informed written consent was obtained.

There were 42 living related allografts, and 22 cadaver allografts. Four cadaver transplants were second grafts while one living related transplant was a second graft. All cadaver recipients received Cyclosporin A; of these there were 16 with 1-DR (CSA-CAD-1DR group) and there were six with zero DR match (CSA-CAD-ODR group). All HLA identical 2-DR match living related recipients (AZA-LRD-2DR group) were given azathioprine. Six other 1-DR match living related recipients (CSA-LRD-NP group) received Cyclosporin A because the stimulation index by MLC was greater than 6.5 in four and because of the preference of the physician in two. The remaining 27 living related allografts were randomized between Cyclosporin A (11 were 1-DR match, the CSA-LRS-1DR group, and two were 2-DR match HLA non-identical, the CSA-LRD-2DR group) and azathioprine, of which there were 14 with 1-DR match (AZA-LRD-1DR group).

Cyclosporin A was given orally at an initial dose of 14mg/kg (except in the first three patients in the CSA-LRD-NP group who received 17mg/kg) starting two days before transplantation then tapered slowly until a dose of 6mg/kg was reached at 90 days. The trough levels of Cyclosporin A were measured by HPLC.

Azathioprine was given at an initial dose of 4mg/kg starting two days before surgery, then tapered to a maintenance dose of 2.5mg/kg at seven days.

Prednisone was given at a dose of 2mg/kg starting two days before transplantation then gradually tapered to 0.33mg/kg.

Conversion was done as follows: on the first day of conversion, azathioprine was started at 2.5mg/kg. At the same time the dose of Cyclosporin A was reduced daily by 1mg/kg and discontinued on the sixth day. Prednisone was increased to 0.66mg/kg on days one to seven, then reduced by 5mg/kg/day every week until the maintenance dose of 0.33mg/kg was reached.

Results

Table I shows occurrences of early and late rejections in various groups. All early acute rejections occurred within six weeks post-transplant; 82 per cent of these occurred within two weeks. Late rejections occurred five to 10 months post-transplant, except in one CSA-CAD-ODR patient whose late rejection was a continuation of a partially controlled early rejection after his second allograft; except for this case and another resistant late rejector and still presently receiving anti-rejection therapy in the AZA-LRD-2DR group, all rejections, both early and late, were promptly controlled by anti-rejection treatment. All late rejectors were biopsied and all showed changes consistent with chronic rejection, except one who presented with nephrotic syndrome whose biopsy revealed changes of acute rejection.

Deaths were due to sepsis at two weeks post-transplant, associated with severe leucopenia due to undetected bone marrow sclerosis in one patient in the

TABLE I. Early and late rejections in 64 allografts

Group	Number of patients	Number of patients with	
		Early rejection (%)	Late rejection (%)
AZA-LRD-2DR	9	2 (22)	2 (22)
CSA-LRD-2DR	2	0	0
AZA-LRD-1DR	14	6 (43)	1 (7)
CSA-LRD-1DR	11	1 (9)	0
CSA-LRD-NP	6	2 (33)	1 (17)
CSA-CAD-1DR	16	2 (12)*	2 (12)
CSA-CAD-ODR	6	4 (67)*	1 (17)
ALL PATIENTS	64	17 (27)	7 (11)

*Significantly different from each other at $p < 0.05$ with the Fisher exact probability test

AZA-LRD-1DR group, disseminated mycosis at one month post-transplant in one patient in the AZA-LRD-1DR group, pulmonary embolism at four months in one patient in the CSA-CAD-1DR group, severe viral hepatitis with post-hepatic cirrhosis, hepatic coma and sepsis in one patient in the CSA-LRD-NP group who died four months post-transplant, and mediastinal lymphoma at nine months in one patient in the CSA-CAD-ODR group. All five graft losses were associated with these deaths. There was no rejection at the time of death except in the case with lymphoma, who had chronic rejection and the leucopenic case in the AZA-LRD-1DR group who had acute rejection nine days before death. Overall actuarial graft survival was 91 per cent at 12 months.

There were more infections within the first four months post-transplant among 41 patients treated with Cyclosporin A than among 23 patients treated with azathioprine. There were 10 patients with pneumonia, four with bronchitis, three with viral hepatitis and five with herpes zoster among the former group, and one, nil, nil and one, respectively, among the latter group; 49 per cent of patients in the former group had at least one of any of the four infections compared with nine per cent in the latter group, a statistically significant difference at $p < 0.01$ with the chi-square test with Yate's correction. When the randomized CSA-LRD-1DR and the AZA-LRD-1DR groups were similarly compared, 73 per cent of patients in the former had at least one of the four infections compared with only seven per cent in the latter, a similarly significant difference at $p < 0.001$ with the Fisher exact probability test.

Six patients had viral hepatitis: two CSA-LRD-1DR patients (both at one month after conversion), one CSA-CAD-1DR patient at four months post-transplant and three CSA-LRD-NP patients (one at 6 months after conversion, and two at 2 months post-transplant). All had clinical remissions from the hepatitis, except one patient in the CSA-CAD-1DR group who had hepatitis two weeks prior to an ultimately fatal episode of pulmonary embolism and terminally had hepatic coma, and one case in the CSA-LRD-NP group who died from hepatic coma and sepsis; both patients who died were among the three who had hepatitis while they were still taking Cyclosporin A.

Excluding patients who had viral hepatitis, 20 of 38 Cyclosporin A patients (12 transiently and 8 persistently) and nine of 23 azathioprine patients (7 transiently and 2 persistently) showed rises of serum glutamic pyruvic transaminase, presumably from hepatotoxicity within four months post-transplant.

Among 41 patients who received Cyclosporin A, eight had early hyperkalaemia (within 2 weeks post-transplant not associated with acute tubular necrosis) and 10 had late hyperkalaemia (beyond 2 weeks). Among 23 patients who received azathioprine, none presented with nephrotoxicity, five had early hyperkalaemia and none had late hyperkalaemia.

Nephrotoxicity manifested as unexplained rises in serum creatinine of 0.9 to 1.7mg/100ml to levels of 2.5 to 3.4mg/100ml in six patients at three to seven months post-transplant. One of these received 17mg/kg Cyclosporin A. All of these patients were converted to Cyclosporin A at four to seven months post-transplant and serum creatinine levels dropped by 0.5 to 1.8mg/100ml within one month after conversion. Three of the six patients with nephrotoxicity had late hyperkalaemia.

Thirty patients were electively converted to azathioprine at four to seven months after transplantation. There were no episodes of rejection within four months after conversion; two had chronic rejection six months after conversion and one had nephrotic syndrome five months after conversion with the picture of acute rejection on biopsy. Serum creatinine did not change by more than 0.3mg/100ml in 18 patients but decreased by 0.4 to 1.8mg/100ml in 12 within one month after conversion; five of the latter did not show later hyperkalaemia or evident nephrotoxicity prior to conversion.

Discussion

We have demonstrated the efficacy of Cyclosporin A as an immunosuppressive agent in combination with steroids in our patient population in both living related and cadaver transplantation. However, the higher incidence of infection among Cyclosporin A recipients than among azathioprine recipients, in contrast to the experience of others, could indicate that our patients were more immunosuppressed than Western patients at equivalent doses. The possibility of reducing the dose of Cyclosporin A or reducing the dose of steroids should be considered.

We have also noted a frequent occurrence of hepatotoxicity with Cyclosporin A as shown by transient, as well as persistent, rises in serum glutamic pyruvic transaminase during the first four months after surgery. Similar findings were noted with azathioprine. However, the deaths from hepatic coma associated with viral hepatitis in two of three patients who were on Cyclosporin A at the onset of hepatitis might indicate increased hepatotoxicity in the presence of viral hepatitis.

Nephrotoxicity as indicated by significant rises in serum creatinine or significant post-conversion decrease in serum creatinine or late hyperkalaemia was noted in 44 per cent of our Cyclosporin A patients.

The nephrotoxicity of Cyclosporin A as well as reservations about its long-term effects [4] have led several workers to convert the immunosuppressive

regimen to azathioprine using varied protocols at varied intervals after transplantation. Frequent occurrences of rejection and graft loss following conversion from Cyclosporin A to azathioprine have been reported among cases converted because of nephrotoxicity or persistent rejection with Cyclosporin A [2,5,6]. More recent reports on elective conversion from Cyclosporin A to azathioprine have yielded similar results [7-9]. However, Tegzess et al reported only one rejection episode in an elective conversion of 18 patients at four months post-transplant.

Our own protocol in elective conversion at four months post-transplant has been similarly demonstrated to be safe and did not result in breakthrough rejection among our patients. Furthermore, renal function improved remarkably within one month after conversion, particularly among those with clinical nephrotoxicity.

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