Early Elimination of Cyclosporine in Kidney Transplant Recipients Receiving Sirolimus Prevents Progression of Chronic Pathologic Allograft Lesions

J.C. Ruiz, J.M. Campistol, A. Mota, D. Prats, J.A. Gutiérrez, A. Castro, J. García, J.M. Morales, J.M. Grynió, J.M. Gómez, and M. Arias

ABSTRACT

Cyclosporine elimination in a regimen including sirolimus has been shown to be a safe and effective approach to improve graft function. Nevertheless, it is still unknown whether the functional benefit of CyA withdrawal coincides with a subsequent reduction in histologic lesions of chronic damage or development of chronic allograft nephropathy. This consideration would forcast a reduction in the rate of long-term graft loss. We analyzed 114 graft biopsies from a subgroup of 57 patients that had been included in a randomized study to eliminate CyA at 3 months posttransplant from a regimen including sirolimus either in group A CyA + SRL vs group B of SRL with CyA elimination at 3 months. Every patient had two biopsies, one at transplantation and another at 1 year. The biopsy reading was performed in a blinded manner by a central pathologist using the Banff 1997 and the CADI classifications. A significantly lower rate of progression of tubular and interstitial chronic lesions between basal and 1-year biopsies was observed for group B patients. In addition, the incidence of new cases of chronic allograft nephropathy during the first year was significantly lower in the group in which CyA had been eliminated at 3 months posttransplant. We conclude that early elimination of CyA in the first months posttransplant, when SRL is used as the main immunosuppressant, reduces the appearance or worsening of chronic histologic lesions, probably as a consequence of long-term CyA toxicity prevention.

CHRONIC ALLOGRAFT NEPHROPATHY (CAN) is the main cause of graft loss after the first year of transplantation with a prevalence of about 60% to 70% among protocol biopsies performed at 2 years posttransplant in patients receiving the calcineurin inhibitors cyclosporine (CyA) or tacrolimus (TRC).[1] These drugs seem to play a role in the development of CAN and subsequent attenuation of long-term graft survival due to their nephrotoxic effects.[2] Sirolimus (SRL) has shown similar efficacy to CsA when used alone with respect to graft rejection rates and short-term graft survival, whether combined with steroids and azathioprine or steroids and mycophenolate mofetil (MMF).[3,4] A low rejection rate and minimization of CyA nephrotoxicity at 3 years were demonstrated in multicenter, randomized, phase III trial currently ongoing at 57 centers in Europe, Canada, and Australia, including 525 patients. The trial compares a control arm (A) using CyA, fixed doses of SRL, and steroids, and an study arm (B) with concentration-controlled SRL and steroids with suspension of CyA at 3 months posttransplant.[5] Using a substudy of this trial, including 70 patients in the ten centers participating in Spain and Portugal, we hypothesized a lower rate of progression of chronic allograft pathologic lesions when CyA was eliminate based upon a retrospective analysis of the information supplied by ten local pathologists.[6] Herein we present the results of a prospective reanalysis of the

From the Hospital Valdecilla (J.C.R., J.M.G., M.A.), Santander, Spain; Hospital Clinic i Provincial (J.M.C.), Barcelona, Spain; Hospital Da Universidade De Coimbra (A.M.), Coimbra, Portugal; Hospital Clínico (D.P.), Madrid, Spain; Hospital Miguel Servet (J.A.E.), Zaragoza, Spain; Hospital Geral de Santo Antonio (A.C.), Porto, Portugal; Hospital La Fe (J.G.), Valencia, Spain; Hospital 12 de Octubre (J.M.M.), Madrid, Spain; and Hospital Bellvitge (J.M.Gr.), Barcelona, Spain.

Address reprint requests to J.C. Ruiz, H.U. Valdecilla, Nephrology Department, Santander 39008, Spain.

0041-1345/03/$–see front matter
doi:10.1016/S0041-1345(03)00612-2

renal biopsies of this subgroup of patients by a central, blinded pathologist.

MATERIALS AND METHODS

One hundred fourteen graft biopsies corresponding to 57 of the subgroup of 70 patients (81%) reported in our previous article[6] were reevaluated by a central pathologist (J.M.G.) in a blinded manner. Every patient had both a pretransplant (basal) and a 1-year biopsy. Twenty-nine cases had been included in group A (CyA + SRL) and 28 in group B (SRL with CyA withdrawal at 3 months post-Tx). Biopsies were reevaluated according to the Banff 1997 and CADI classifications. Both groups were compared for every individual lesion. Three chronicity scores (CS) were calculated as the sum of the chronic items (Banff CS1: cg + ci + ct + cv; Banff CS2: cg + ci + ct + cv + ah; and CADI CS: i + f + m + g + t + v). Differences in renal function at 1 year were reported in a previous study.[6] We considered the presence of progression when any given Banff or CADI code was higher in the 1-year biopsy than in the transplant (basal) biopsy; when it was equal or lower it was considered nonprogression. Chronicity scores were analyzed in the same way. The percentage of patients with progression of chronicity findings in every group (individual lesions and CS) was compared using the chi-square test. We also calculated the prevalence of CAN (diagnosed according to Banff 1997 criteria) at the moment of transplantation versus 1 year, and the incidence of new cases of this entity that developed during the first year (patients with absence in basal biopsy and presence of CAN at 1 year) in every group.

RESULTS

The progression rates of Banff chronic lesions for patients in groups A and B, respectively, were: cg, 0% vs 9.1%; ci, 70% vs 40.9%; ct, 70% vs 47.8%; cv, 29.4% vs 25%; and ah, 10.5% vs 19%, whereas progression rates of CADI lesions were: i, 52.6% vs 54.5%; f, 68.4% vs 40.9%; m, 21.1% vs 23.8%; g, 5.3% vs 14.3%; t, 68.4% vs 45.5%; and v, 31.3% vs 23%. When CS were considered the following rates of progression were observed: Banff CS1, 76.5% vs 31.3% ($P < .05$); Banff CS2, 76.5% vs 37.5% ($P < .05$); and CADI-CS, 75% vs 43.8%. The prevalence of CAN at 1 year was higher in group A (70.8% vs 59.3%; P = NS) despite higher scores in group B at the time of transplantation (9.5% vs 21.7%). For this reason, the incidence of new cases of CAN during the first year was significantly higher in group A (65%) when compared with group B (30.8% of patients; $P < .05$).

DISCUSSION

Early cyclosporine withdrawal using sirolimus is followed not only by an improvement in renal function, but also by a reduction in the rate of progression of chronic pathologic allograft lesions and in the appearance of new cases of CAN. This effect is especially important in the case of tubular and interstitial lesions, probably as a consequence of a reduction of CyA nephrotoxicity without an increase in the immunologic response against the allograft. It is possible that this beneficial effect might be responsible for better graft outcome after longer follow-up periods.

REFERENCES

1. Solez K, Vincenti F, Filo RS: Transplantation 66:1736, 1998
2. Paul LC: Kidney Int 56:783, 1999
3. Groth CG, Bäckman L, Morales JM, et al: Transplantation 67:1036, 1999
4. Kreis H, Cisterne JM, Land W, et al: Transplantation 69:1252, 2000
5. Johnson R, Kreis H, Oberbauer R, et al: Transplantation 72:777, 2001
6. Ruiz JC, Campistol JM, Mota A, et al: Transplant Proc 34:92, 2002