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Long-term results of a prospective randomized study comparing two immunosuppressive regimens, one with and one without CsA, in low-risk renal transplant recipients

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Abstract Due to the nephrotoxicity of cyclosporin A (CsA), its benefit on long-term graft survival remains controversial, especially in low-risk patients. Here we report the 12-year results of a calcineurin-inhibitor-free regimen. One hundred and seventeen low-risk kidney recipients were prospectively randomized to maintenance therapy with either a combination of azathioprine and prednisone (group NoCsA, $n=58$), or with cyclosporine, azathioprine, and prednisone (group CsA, $n=59$). Both groups received induction therapy with anti-lymphocyte globulins (ALG). Twelve-year patient survival was 75% and 82.5% in the CsA and NoCsA groups, respectively [$P=$ not significant (NS)]. Twelve-year graft survival was 59% and 56% ($P=$NS) in the CsA and NoCsA groups, respectively (NS). Transplant rejection rates were similar in both groups. Mean serum creatinine levels after 10 years were 161 and 136 μmol/l in the CsA and NoCsA groups, respectively. Rejection-free patients of the CsA group had poorer renal function (168 μmol/l) than those of the NoCsA group (121 μmol/l; $P=0.0060$). We concluded that a 12-year graft survival of 56% and a graft half-life of 15 years can be achieved without the primary use of a calcineurin inhibitor in low-risk patients receiving ALG. Patients treated with CsA had poorer graft function at 12 years.

Keywords Renal transplantation · Cyclosporine · Anti-lymphocyte globulin · Graft survival · Long-term outcome

Introduction

The introduction of cyclosporin A (CsA), the first calcineurin inhibitor (CNI), approximately 20 years ago, has resulted in a significant decrease of early acute rejection and an improvement of short-term graft survival [1, 2]. However, the benefit of long-term graft survival has been more modest [3, 4, 25], which is most probably due to the irreversible chronic nephrotoxicity caused by the CNI. Many studies have emphasized this nephrotoxicity associated with the use of CNIs [3, 4]. More recently, a study showed that histopathological signs of CNI-associated nephrotoxicity at 2 years was one of the most significant predictors for chronic allograft nephropathy [33]. Furthermore, numerous studies have reported beneficial effects of conversion from CsA to AZA on – among others – long-term renal function [13, 17, 19, 22, 24, 32].

Altogether, those data strongly suggest that CNI-associated nephrotoxicity might have a major impact on long-term graft survival. In contrast, some other studies have suggested that rejection episodes triggered by the withdrawal of CsA might outweigh the benefit obtained on renal function [6, 7, 10, 21]. However, there is evidence

that the withdrawal of a drug can induce a rebound effect. Consequently, the withdrawal of a drug is not equivalent to its not being used it [14]. Thus, the design of CNI-free immunosuppressive regimens that could efficiently prevent acute rejection is highly desirable, especially for patients receiving a cadaveric allograft from suboptimal donors or for patients at risk of delayed graft function. The recent introduction of non-nephrotoxic and potent immunosuppressive drugs has added new alternatives allowing us to avoid the use of CNIs, but as these alternative drugs have only recently become available, their long-term benefit remains to be established.

Although many authors have analyzed the kidney graft outcome after CsA withdrawal [10, 15, 16, 20, 21, 24, 27, 29, 31, 32], trials that do not include any CNIs are quite rare [8, 18]. Therefore, the real impact of CNIs on long-term graft outcome is difficult to assess.

Before the widespread use of CsA, several studies had shown that adding polyclonal anti-lymphocyte globulins (ALG) decreased the acute cellular rejection rate and improved 1-year allograft survival, compared with regimens including only azathioprine (AZA) and prednisone (PRED) (review in [34]). Therefore, we hypothesized that low-risk patients receiving polyclonal ALG might be spared CsA maintenance therapy. Herein, we report for the first time, the long-term results of a randomized prospective study in which we compare two immunosuppressive regimens, one with and one without CsA in low-risk patients who all received induction therapy with polyclonal ALG.

Patients and methods

Patients

From December 1986 to January 1989, 117 consecutive Caucasian adult recipients of a first cadaveric renal allograft were enrolled in this prospective randomized study. HLA-immunized and diabetic recipients were excluded. Before undergoing transplantation, all patients received at least three units of blood. HLA class I and II alleles were determined by standard serological techniques. A negative standard T-cell cross-match between the recipient and donor was required. Follow-up was for at least 12 years for each patient. Clinical outcomes were recorded at 1, 5, and 12 years after transplantation.

At the time of transplantation, the patients were randomized to maintenance therapy with AZA and PRED, plus CsA added on day 14 (CsA group, $n = 59$) and to AZA and PRED alone (NoCsA group, $n = 58$).

Immunosuppression

All patients received induction therapy with horse anti-lymphocyte globulins (ALG, Imtix, Pasteur-Mérieux) 5 mg/kg per day for 14 days in combination with AZA (1.5 mg/kg per day) and steroids (1 mg/kg per day). Oral PRED 1 mg/kg per day was given during the first month and then tapered to a maintenance dose of 15 and 10 mg/day in the NoCsA and CsA groups, respectively. During the 12-year follow-up, the mean AZA dose was 2–3 mg/kg per day (≤ 150 mg/day) in the NoCsA group, and 1.5 mg/kg per day in the CsA group. CsA medication (Sandimmun) was started on post-transplant day 14 at a dose of 6–8 mg/kg per day. Thereafter, dosage was adjusted to keep the trough CsA blood levels (assessed by a polyclonal radioimmunoassay kit) between 200 and 600 ng/ml, during the first 6 months and from 150–400 ng/ml thereafter. When the monoclonal antibody assay became available, trough blood levels were kept between 100 and 150 ng/ml after the first 6 months.

Acute rejection was defined as a serum creatinine level increase by 30% or more over baseline, not ascribable to any other identifiable cause. In most cases, the diagnosis was confirmed by a renal biopsy. Patients with delayed graft function underwent weekly renal biopsies. Rejection episodes were treated in both groups with high-dose methylprednisolone. Patients who failed to respond to this treatment received 5 mg/day Orthoclone OKT3 monoclonal antibodies for 10 days, or 3–5 mg/kg per day ALG for 7 days. Patients in the NoCsA group who experienced either a steroid-resistant or a second rejection episode were given CsA.

Study endpoints

Primary endpoint of this study was 12-year graft survival. We also assessed the composite endpoint of treatment failure defined by graft loss, death, or changes in the immunosuppressive treatment primarily assigned at randomization (introduction of CsA in patients primarily randomized to the NoCsA group or withdrawal of CsA in patient randomized to the CsA group). Secondary endpoints included 1- and 5-year graft survival, 12-year patient survival, numbers of acute rejection episodes, numbers of patients switched from their initial regimen to the other regimen, incidence of hypertension and malignancies, serum creatinine, calculated creatinine clearance (Cockroft), fasting blood glucose, and serum cholesterol and triglyceride levels at 12 years.

Statistical analyses

All analyses were performed on an intention-to-treat basis. The standard two-sample t test was used to test differences in means, and Pearson's chi-square test of association to test differences in proportions. Patient survival was the time from transplantation to patient death, and graft survival, the time from transplantation to graft failure or patient death. Survival curves were generated with the Kaplan-Meier (product-limit) method and were compared using the generalized log-rank test. Transplant half-life values in the two groups were compared by the method reported by Takiff et al. [35]. P values under 0.05 were considered statistically significant.

Results

Patient and graft survival

Patient characteristics at baseline in the two groups are shown in Table 1. Mean age, gender ratio, distribution of the native kidney diseases, number of HLA mismatches, cold ischemia times, incidence of delayed graft function, or donor age were not statistically different in the two groups. Patient survival at 1, 5, and 12 years (Fig. 1) was 98%, 90%, and 82.6%, respectively, in the NoCsA group and 98%, 90%, and 74.8%, respectively, in the CsA group ($P = 0.38$). Eight deaths occurred in the NoCsA group; the cause of death was an infection (four patients), cancer (two patients), and cardiovascular

Table 1 Characteristics of patients at the time of renal transplantation

Clinical parameters	Double therapy	Triple therapy
Total number	58	59
Age (years)	40 ± 11.6	40.6 ± 10.2
Men *(n)*	36	40
Women *(n)*	22	19
Original disease *(n)*		
Glomerulonephritis	32	35
Pyelonephritis	6	4
Vascular disease	6	3
Congenital disease	4	5
Unknown	10	12
HLA A-B-DR mismatches/patient	3.42 ± 4 ± 1.22	3.11 ± 0.94
Cold ischemia time (h)	22.3 ± 6.7	23.7 ± 6.2
Donor age (years)	36 ± 9.3	38 ± 8.5
Acute tubular necrosis (%)	28	34

disease (two patients). There were 12 deaths in the CsA group; six were due to cardiovascular diseases, two to infections, two to solid cancer, one to lymphoma, and one to a car accident.

Actuarial graft survival at 1, 5, and 12 years (Fig. 2) was 89%, 75%, and 56%, respectively, in the NoCsA group, and 91%, 82%, and 59%, respectively, in the CsA group ($P = 0.41$). In the NoCsA group, 16 patients lost their transplant, due to chronic allograft dysfunction ($n = 11$), acute rejection ($n = 3$), recurrence of focal and segmental glomerular sclerosis ($n = 1$), or early arterial thrombosis ($n = 1$). Ten patients in the CsA group lost their graft, due to chronic allograft dysfunction ($n = 7$), acute vascular rejection ($n = 1$), or recurrence of membranoproliferative glomerulonephritis ($n = 2$).

Among the patients with a functioning graft at 1 year after transplantation, graft half-life was 15.25 years (range 13.6–16.16) in the NoCsA group, and 16.35 years

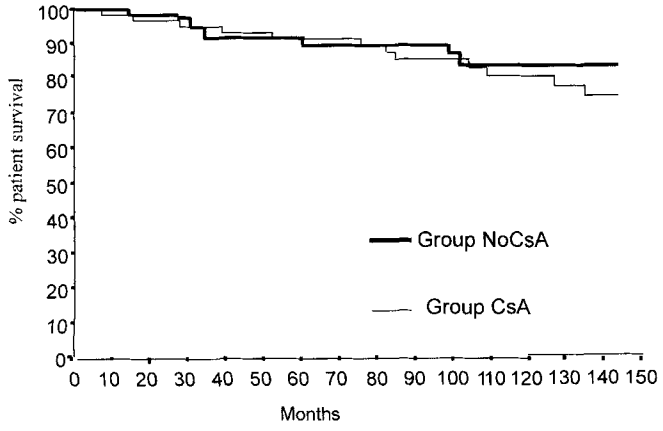

Fig. 1 Actuarial patient survival in group NoCsA, randomized without CsA (*bold line*), and in group CsA, randomized to receive CsA (*thin line*). Statistical analysis by log-rank test showed $P = 0.37$

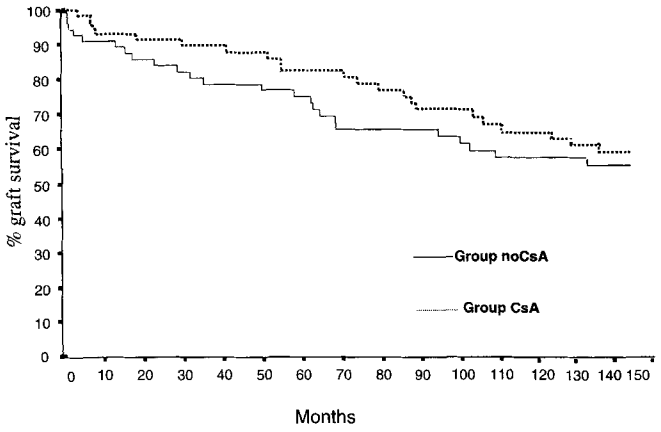

Fig. 2 Actuarial graft survival in group NoCsA, randomized without CsA (*thin line*), and in group CsA, randomized to receive CsA (*dotted line*). Statistical analysis by log-rank test showed $P = 0.49$

(range, 15.5–16.9) in the CsA group [P = not significant (NS)] (Fig 3).

Acute rejection occurred in 56% of patients in the NoCsA group and in 52% of the CsA group (P = NS). The mean numbers of acute rejection episodes per patient were 1.6 ± 1.03 and 1.49 ± 1.01 (P = NS) in the NoCsA and CsA groups, respectively. The number of steroid-resistant rejection episodes requiring OKT3 or ALG therapy was also similar in the two groups (eight in the NoCsA group and nine in the CsA group).

Twelve-year mean serum creatinine levels in the NoCsA and CsA groups were 136 ± 105 μmol/l and 161 ± 95 μmol/l, respectively ($P = 0.23$). Calculated creatinine clearances were 48 ± 20 ml/min and 39 ± 18 ml/min, respectively ($P = 0.22$). To evaluate better the direct impact of the long-term use of CsA on renal function, we also compared the creatinine levels at 12 years in rejection-free patients who were still receiving the initial

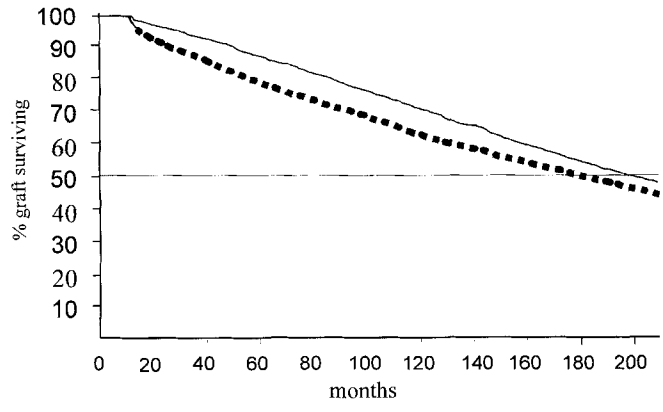

Fig. 3 Half-life of kidney grafts surviving after 1 year in group NoCsA, randomized without CsA (*bold dotted line*), and in group CsA, randomized to receive CsA (*thin line*)

treatment assigned at randomization. Twenty-six patients from the CsA group and 21 from the NoCsA group fulfilled those criteria. The mean serum creatinine level was significantly lower in rejection-free patients of the NoCsA group (121 ± 43 μmol/l) than in those of the CsA group (168.5 ± 76 μmol/l; $P = 0.0060$).

Clinical and biological events

Severe infections requiring hospitalization (including clinical cytomegalovirus disease) occurred in 18.9% of the patients in the NoCsA group and 20.7% of the CsA group. Cancer was diagnosed in 12% and 13.5% of the patients in these groups, respectively (P = NS). However, patients who had received CsA ($n = 80$) at some point in the study had a higher rate of malignancies than those who never received CsA (17% to 2.7%, $P = 0.04$).

The 12-year prevalence of hypertension was similar in the NoCsA and CsA groups (70% and 73.5%, respectively; P = NS). The mean number of anti-hypertensive medications used per patient was 1.2 ± 1.0 in the NoCsA group and 1.4 ± 1.0 in the CsA group. The incidence of cardiovascular events (myocardial infarction, heart ischemia, arrhythmias, angina, and/or occlusive peripheral arterial disease) was 11.5% in the NoCsA group vs 13.8% in the other (P = NS). Likewise, at 12 years, there was no statistically significant difference between the two groups regarding the mean serum cholesterol levels (4.8 ± 2.5 vs 5.4 ± 1.9 mmol/l, in the NoCsA and CsA group, respectively), and the triglyceride levels (1.4 ± 0.9 vs 1.8 ± 0.7 mmol/l, in the NoCsA and CsA group, respectively). New onset of de-novo diabetes after transplantation was 2.5% in the NoCsA group and 3.5% in the CsA group (P = NS).

Changes in therapy

Thirty-two patients were switched from their initial regimen to the other regimen within 6 months (NoCsA group) or 1 year (CsA group) after transplantation. After 12 years of follow up, 62% of patients of the NoCsA group and 83% of the CsA group were still assigned to their original regimen. Twenty-two of the patients randomized to the NoCsA group (38%) were given add-on CsA therapy (according to the protocol for 20 patients, because of recurrent or steroid-resistant acute rejections, and because of AZA-induced neutropenia for two other patients). CsA was discontinued in ten patients (17%) primarily randomized to the CsA group, because of histological changes suggesting chronic CsA nephrotoxicity. However, treatment failure rates, as defined by graft loss, death, or changes in the treatment primarily assigned at randomization, were not statistically different at 12 years: 58.5% and 50%, respectively, in the NoCsA and CsA group ($P = 0.1$).

Discussion

The adoption of CNIs (CsA or tacrolimus) by most transplant centers as the mainstay of immunosuppression has reduced graft failure rates during the first year after transplantation [1, 2]. Nevertheless, many studies have pointed out their nephrotoxic effects [3, 4], that may contribute to the long-term development of renal function impairment and to subsequent graft loss. Thus, the design of CNI-sparing protocols seems highly desirable. Some CNI-sparing studies have reported a significantly increased risk of acute rejection after CsA withdrawal [10, 16, 21, 27], whereas one has reported that dose reduction of CsA [in patients receiving mycophenolate mofetil (MMF)] was safe but did not improve renal function [30]. In contrast, other reports showed improvement of long-term renal function after patients' conversion from a cyclosporine/steroid-based regimen to AZA/steroids or MMF/steroids [17, 19, 22, 24, 32]. Long-term results of randomized therapeutic protocols primarily devoid of CsA have been reported very rarely [8, 18], because CsA rapidly became the cornerstone immunosuppressive drug for most centers in the past 15years. Although CNI-free regimens, using some newly introduced drugs are currently under investigation [11, 12, 23], the long-term tolerance and benefit of such strategies are not known.

Fifteen years ago, we initiated a randomized study to compare a CNI-free regimen with another one including CsA in low-risk patients. As far as we know, this study is the first to compare the long-term results of two sequential regimens both including anti-lymphocyte globulins as induction therapy, followed by either a triple therapy (AZA, Pred, CsA) or a double therapy (AZA and Pred) as maintenance treatment. Our study indicated that a 12-year graft survival rate of 56% and a graft half-life of 15 years could be achieved without the primary use of a CNI in low-risk patients. Furthermore, it showed that the 12-year graft survival rate was statistically equal in both groups. Likewise, the rates of acute cellular rejection in the two groups were not statistically different, and although they would appear unacceptable today, they were within the range of other studies of the period [26]. Thus, the long-term results of the present study, combined with recent data on the short-term outcome of CNI-free regimens including Sirolimus and MMF [11, 23], strongly encourage the investigation of further protocols primarily devoid of CNIs.

The "cross-over" patient rate of 27% in the present study was inside the range of those reported in other

open-label trials comparing triple-drug and double-drug therapy [28]. The number of patients that were switched to the other regimen was higher in the group randomized to treatment without CsA than in the other group (38% vs 17%). This is obviously explained by the design of the protocol that required the introduction of CsA in the NoCsA group after the second acute rejection episode. However, when these changes in therapy were included in the composite endpoint, treatment failure rates of both groups were statistically equal, at the end of the study.

At 12 years, renal function tended to be better in the NoCsA group (creatinine 136 ± 105 vs 161 ± 95 μmol/l), although it was not statistically significant. The difference became highly significant when we compared 12-year creatinine levels in rejection-free patients who were still receiving the initial treatment assigned at randomization (121 ± 43 vs 168.5 ± 76 μmol/l; $P = 0.0060$). These observations confirm the nephrotoxicity associated with the long-term use of CNIs, and are in line with previous studies [17, 19, 22, 24, 32] showing that conversion from CsA to AZA resulted in renal function improvement.

The incidence of clinical events such as hypertension, mean total cholesterol and triglyceride levels in the intention-to-treat analysis was not significantly different in the two groups. Those findings were unexpected, since CsA is known to induce or aggravate post-transplant hypertension and hyperlipidemia. It may be ascribable to the higher doses of PRED in the patients primarily randomized to the regimen without CsA and to the fact that CsA had to be given to some patients primarily randomized to the NoCsA group. In addition, the incidence of cancer was significantly higher in patients exposed to CsA than in those who did not receive CsA at all (17% vs 2.7%, $P = 0.03$). This is in keeping with the study by Dantal et al. [5] that reported a higher incidence of malignancy when CsA was used at standard doses, than when it was used at lower doses.

Finally, it is noteworthy that the short- and long-term graft survival rate in the present study compared favorably with previous reports [2, 9, 18, 28], for both groups. Several reasons may account for this finding: high-risk patients (diabetic, second graft, immunized, non-Caucasian) were excluded; all the patients were transfused prior to undergoing transplantation and were relatively well HLA-matched. More importantly, and in contrast with previously cited reports, both groups in our study had received induction therapy with polyclonal ALG, and recent meta-analysis 34] has reported that those polyclonal antibodies significantly improved 2-year renal allograft survival.

In conclusion, this study indicated that a graft half-life of 15 years and graft survival rates of 75% and 56% at 5 and 12 years, respectively, could be achieved without the use of a CNI as a first-intention treatment, in low-risk patients receiving ALG as induction therapy. In addition, our study showed that long-term use of CsA was associated with a poorer graft function at 12 years. These results, together with recent data on the short-term outcome of CNI-free regimens using Sirolimus and MMF, should strengthen the current wave of interest in CNI-free immunosuppressive regimens.

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