



Low-Dose Versus High-Dose Cyclosporine Induction Protocols in Renal Transplantation

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ABSTRACT

Background. Current immunosuppressive therapies are effective to prevent acute rejection episodes (ARE) and graft loss following renal transplantation. Newer agents now make it possible to develop equally efficacious but better tolerated, less toxic strategies. We compared the efficacy of early low- versus high-dose cyclosporine (CsA) induction therapy in living donor renal transplantation.

Methods. In this single-center study, 90 consecutive recipients of living donor kidney transplants between November 2002 to October 2003 including 51 females and mean average age of 48.23 years were treated with either CsA (5 mg/kg/d) plus mycophenolate mofetil (MMF; 30 mg/kg/d) and prednisolone (1 mg/kg/d; group 1; n = 42); or CsA (8 mg/kg/d) plus MMF (30 mg/kg/d) and prednisolone (1 mg/kg/d; group 2; n = 48). The 2 groups were matched with respect to age, sex, underlying renal diseases, pretransplantation dialysis period, number of transplantations, and panel-reactive antibody tests. CsA dose tapering was initiated in the 2 group 3 months after transplantation. At the end of the first year, the CsA dose was 3.5 ± 0.65 mg/kg in group 1 and 3.4 ± 0.34 mg/kg in group 2. Prednisolone was tapered within the first 2 months, reaching 10 mg/d in all patients. The MMF dose remained unchanged. The 2 groups were compared with respect to ARE, patient and graft survivals, and clinical outcomes within 2 years after transplantation.

Results. There were no significant differences between the 2 groups with respect to clinical outcomes, including 2-year patient survival (97.62% vs 97.92%; $P = .76$), 2-year graft survival (80.32% vs 80.41%; $P = .82$), ARE (47.61% vs 52.08%; $P = .09$), or length of immediate postsurgical hospital stay, number of readmissions, total hospitalization days, posttransplantation diabetes mellitus, and infectious, cardiovascular, gastrointestinal, and hematologic complications. There was more hypertension (67.5% vs 50.23%; $P = .007$), hypertriglyceridemia (45.5% vs 32.64%; $P = .005$), and elevated liver enzymes in group 2 (12.5% vs 7.14%; $P = .018$).

Conclusions. Compared with 8 mg/kg CsA induction therapy, the lower doses of CsA were effective, well tolerated, and safe with relatively fewer side effects.

THE ADDITION OF mycophenolate mofetil (MMF) to an immunosuppressive regimen of cyclosporine (CsA) and prednisone has reduced the rejection rate during the first 6 months after renal transplantation.¹⁻⁴ In 3 "pivotal" trials, designed to investigate the efficacy of MMF when added to standard therapy, patients were treated with full doses of CsA. Although there was no clear increase in the incidence of side effects related to overimmunosuppression, the results gave rise to concerns regarding the long-term safety of the drug regimen.^{1,2} One possible way to reduce

the risk of overimmunosuppression is to lower the CsA dose. If this would not hamper the efficacy of the regimen, it might have the benefit of a reduction in CsA-related side

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Table 1. Patient and Donor Characteristics

Characteristic	High-Dose CsA	Low-Dose CsA
Number	48	42
Gender (M/F)	22/26	20/22
Age (y)	47.12	49.33
Weight (kg)	69.12	71.18
Primary disease (%)		
Chronic glomerulonephritis	19	21
Diabetes mellitus	18	19
Chronic pyelonephritis	15	17
Cystic disease	12	10
Renovascular disease	4	3
Other	10	11
Unknown	22	19
Hemodialysis/CAPD/no dialysis	43/4/1	39/3/0
PRA (median/range)	1/20	1/20
Donor gender (M/F)	35/13	27/15
Donor age (y)	29.26	27.45

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; PRA, panel-reactive antibodies.

effects, such as nephrotoxicity, hypertension, and delayed graft function, which frequently complicate the course. With a reduced CsA dose, the differentiation between rejection and CsA nephrotoxicity also might be easier. Finally, a reduction in CsA dose may partly compensate for the increased costs of medications caused by the addition of MMF. In this clinical trial, renal allograft recipients were randomized to treatment with a high or a low dose of CsA in combination with MMF and prednisolone.

PATIENTS AND METHODS

Adult recipients of a first renal transplant from a living donor were eligible for this study. The study design was approved by the institutional review boards of the university, and written informed consent was obtained from all participants.

Immunosuppression

From 1 day before surgery, CsA was given orally (8 mg/kg/d) in the high-dose group and 5 mg/kg/d in the low-dose group with adjustments to reach a target trough level during the first 3 months of 300 ng/mL (250–350 ng/mL) in the high-dose group and 150 ng/mL (125–175 ng/mL) in the low-dose group. From 3 to 12 months the target trough level was 150 ng/mL in both groups. The microemulsion formulation of CsA (Neoral, Novartis) was used in all patients. CsA whole blood levels were measured with an enzyme-multiplied immunoassay technique. MMF (Cell cept, Roche) was administered at 30 mg/kg/d. Dose reduction or interruption of MMF treatment was allowed in cases of leukocytopenia, or severe infection or gastrointestinal side effects. Methylprednisone (500 mg intravenously) was delivered during the first 3 days followed by an oral dose of 1 mg/kg/d from days 4 to 10, tapering gradually to 0.15 mg/kg/d at 3 months. The last dose was continued thereafter. Induction therapy with anti-T-cell preparations was not used. Rejections were treated primarily with methylprednisolone (500 mg intravenously) for 3 consecutive days. In cases of steroid-resistant rejection, anti-T-cell therapy was given (rabbit polyclonal antithymocyte globulin).

Additional Medications

All patients received prophylaxis for peptic ulcers (ranitidine 150 mg once daily) and *Pneumocystis carinii* pneumonia (cotrimoxazole 480 mg once daily). CMV prophylaxis with ganciclovir was prescribed during anti-T-cell therapy.

Assessments

At baseline, we obtained the medical history, physical examination, routine laboratory tests, lipid profile, and histocompatibility data. Every month, we recorded the vital signs, body weight, and results of routine laboratory measurements. Data on rejection episodes, CsA nephrotoxicity and dialysis requirements, concomitant medications, adverse events, hospital admissions, and infections were recorded throughout the entire study period. A biopsy was performed in cases of deteriorating graft function without an obvious pre- or postrenal cause. No protocol biopsies were performed. Delayed graft function was defined as the need for one or more dialysis sessions more than 24 hours post-operatively. Infections were classified using the Centers for Disease Control and Prevention's definitions for nosocomial infections.⁵

Randomization Procedure

Shortly before renal transplantation patients were randomly assigned to one of the treatment groups in a 1:1 ratio. The randomization was performed by opening a sealed envelope with the lowest available study number.

Endpoints

The primary endpoints were the incidence of biopsy-proven acute rejection or CsA nephrotoxicity during the first 3 months. CsA nephrotoxicity was defined as an otherwise unexplained rise in serum creatinine of more than 25% above the previous level, which was reversible after lowering the CsA dose. Secondary endpoints included time to first acute rejection, number of acute rejection episodes (ARE) within the first 3 months, number of biopsies, incidence and duration of delayed graft function, and graft function at 1 and 3 months. All endpoints also were assessed at 6, 12, and 24 months.

Statistical Analyses

Results are given as mean values and SDs unless stated otherwise. The statistical analyses were performed on an intention-to-treat basis. Comparison of continuous variables between the groups was performed using the Wilcoxon rank sum test. Categorical variables were analyzed with the chi-square test. Comparison of time to first

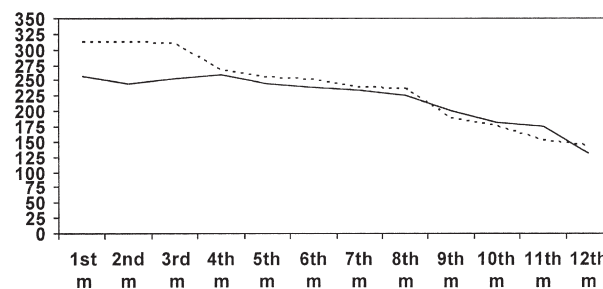


Fig 1. CsA blood level (ng/mL) in high-dose (---) and low-dose CsA during the first 12 months after transplantation.

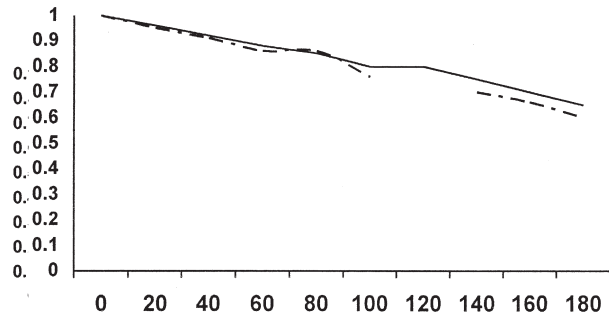


Fig 2. Rejection-free survival in the first 3 months in the high-dose (---) and low-dose (—) groups (Kaplan-Meier curves).

rejection was performed using the Kaplan-Meier procedure with log-rank testing. $P \leq .05$ was considered significant. Calculations were performed using SPSS software.

RESULTS

Between November 1, 2002, and October 31, 2003, 90 patients were enrolled. The demographic data of the patients are summarized in Table 1, showing no significant differences between the groups.

CsA Levels

In accordance with the study design, CsA levels were significantly different between both groups during the first 3 months. At 6 months, both CsA dose and CsA levels were not different between the groups (Fig. 1).

Rejections and Biopsies

The incidence of rejection within the first 12 months was 47.61% in the low-dose and 52.08% in the high-dose groups ($P = .09$; not significant). Moreover, the median time to the first ARE was similar in both groups: 15 and 9 days, respectively (not significant; Fig 2). In all cases, first-line antirejection

treatment consisted of a course of methylprednisolone. Treatment for a rejection was administered in 36% of patients in the high-dose group and 30% of these in the low-dose group (not significant). Treatment with one course of methylprednisolone was sufficient in 66% of patients in the high-dose group and 67% in the low-dose group. In 4 patients in the high-dose group and 1 patient in the low-dose group, we administered additional corticosteroids. In 24% of patients in the high-dose group and 27% in the low-dose group, methylprednisolone treatment was followed by anti-T-cell therapy because of steroid-resistant rejection.

Graft Failure, Patient Death, and Protocol Failure

Within 6 months, graft failure occurred in 4% of the high-dose group and 5% of the low-dose group (not significant). The reasons for graft loss were not different between the groups. Patient death with a functioning graft occurred in 3% patients in the high-dose group and 2% of those in the low-dose group (not significant). In 9% of the high-dose and 11% of the low-dose group, cessation or interruption of one or more of the immunosuppressive drugs was judged necessary for clinical reasons. CsA was discontinued in 2 and 1 patients, MMF 1 and 2 patients, and prednisone in 2 and 0 patients, respectively.

Graft Function

Two-year graft survivals were equal in the high- and low-dose groups (Fig. 3). The median duration of dialysis treatment in these patients also was similar in both groups: median, 10 days (ranges, 1–35 and 1–44 days, respectively; not significant). At all time points during follow-up, serum creatinine (Fig. 4) and proteinuria were comparable in both groups. Episodes of CsA nephrotoxicity occurred in 8% of the high-dose group and 3% of the low-dose group ($P = .06$). Episodes of graft dysfunction that resulted in performing a biopsy tended to occur more frequently among the

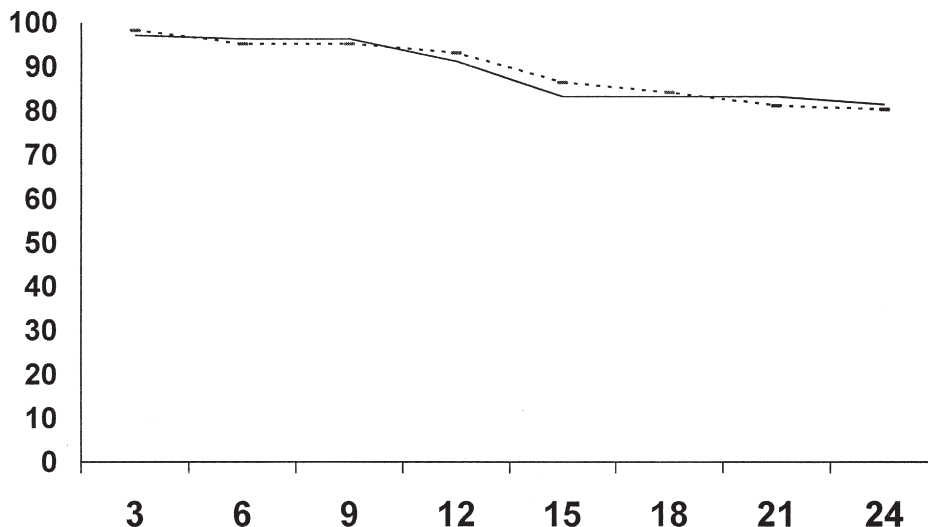


Fig 3. Two-year graft survivals in the high-dose (----) and low-dose (—) groups (Kaplan-Meier curves).

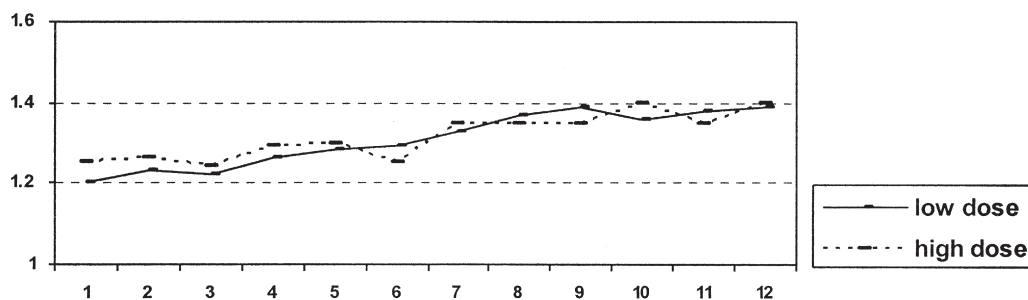


Fig 4. Plasma creatinine (mg/dL) during the first 12 months after transplantation.

high-dose group: number of biopsies per patient, 0.56 vs 0.39 ($P = .09$).

BP, Infectious, Gastrointestinal, and Cardiovascular Complications

There were no significant differences between the 2 groups with respect to the length of immediate postsurgical hospital stay (mean, 23.11 vs 21.25 days), number of readmissions (0.78 vs 0.83 per patient per year), posttransplantation diabetes mellitus or infectious, cardiovascular, gastrointestinal, or hematologic complications. There were more patients experiencing hypertension (67.5% vs 50.23%; $P = .007$), hypertriglyceridemia (45.5% vs 32.64%; $P = .005$), and elevated liver enzymes (12.5% vs 7.14%; $P = .018$) among the high-dose group.

DISCUSSION

The results of this prospective trial indicated that among patients treated with CsA, MMF, and prednisone, prescribing a lower-than-usual dose of CsA did not increase the incidence of ARE. Our findings suggest that MMF can exert a so-called “CsA-sparing” effect. In agreement with the aim of the study protocol, there was a significant, potentially meaningful difference in CsA levels and doses between the 2 groups during the first 3 months. Furthermore, nearly 90% of all analyzed patients were treated according to the study protocol during the full 6 months. Taken together, it seems unlikely that insufficient adherence to the study design obscured a conceivable detrimental effect of a lower target CsA level on rejection incidence. Patient and graft survivals in our study were comparable to the data in the 3 “pivotal” studies.¹⁻³ When designing the study protocol, we expected to find a difference in the incidence of CsA-related side effects between the treatment groups. Several studies indicate that avoidance of CsA during the first postoperative days, by treating the patients with induction therapy with antilymphocyte antibodies, results in an earlier recovery of delayed graft function and overall better graft function.⁶ The same could be true for the early use of a low dose of CsA.⁷ In this study, however, we did not observe a difference in the incidence or duration of delayed graft function or in dialysis duration between the groups. The use of CsA is frequently accompanied by side effects, such as hypertension, hyperlipidemia, neurologic symptoms, and hirsutism, requiring additional therapy in the

majority of patients.⁸ The incidence of these side effects possibly could be lowered by reducing the CsA dose. In our study, more HTN, hypertriglyceridemia and elevated liver enzymes occurred among the high-dose group. By lowering the CsA dose, a significant reduction in the costs of CsA could be obtained. However, the overall effect of the introduction of MMF on the costs remains uncertain, because MMF leads to a major increase in the costs of immunosuppressive maintenance therapy. Conversely, by lowering the rejection rate, substantial savings in the costs of hospitalization and anti-T-cell therapy can be achieved.

In conclusion, we demonstrated that the addition of MMF to an immunosuppressive regimen consisting of CsA and prednisone allowed the use of a lower-than-usual dose of CsA during the first 3 months after renal transplantation without increasing the risk of acute rejection. According to some evidence for a decline in the incidence of CsA nephrotoxicity, the reduction in CsA dose was accompanied by a decrease in other CsA-related side effects.

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