Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: One-year results of a 2-center prospective randomized trial

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Objectives: Cyclosporine (INN: ciclosporin) A or tacrolimus have been used mostly in combination with azathioprine as primary immunosuppression after lung transplantation. Benefit or risk deriving from the combination with mycophenolate mofetil are yet unknown.

Methods: In a prospective, 2-center, open randomized trial, the combination of cyclosporine A, mycophenolate mofetil, and steroids was compared with tacrolimus, mycophenolate mofetil, and steroids as primary therapy after primary lung transplantation. All patients underwent induction therapy with rabbit antithymocyte globulin for 3 days. The 2 groups were compared with regard to patient survival, freedom from acute rejection, bronchiolitis obliterans, infectious episodes, and side effects.

Results: Between September 1997 and April 1999, 74 lung transplant recipients were randomized to receive either cyclosporine A (n = 37) or tacrolimus (n = 37). Groups were comparable with regard to age, sex, transplant procedure, and cytomegalovirus match. Mean follow-up was 507 ± 258 and 508 ± 248 days, respectively. Six- and 12-month survival was similar in both groups (89% vs 84% and 82% vs 71%, respectively; $P = .748$ at 12 months). Two patients from the cyclosporine A group were retransplanted. Freedom from acute rejection at 6 and 12 months was comparable between groups (46% vs 51% and 35% vs 46%, respectively; $P = .774$ at 12 months). The mean number of treated acute rejection episodes per 100 patient-days was higher in the cyclosporine A than in the tacrolimus group, but the difference was not statistically significant (0.32 ± 0.42 vs 0.22 ± 0.30, respectively; $P = .097$). Four patients from the cyclosporine A group had to be switched to tacrolimus to control ongoing rejection, whereas no patient from the tacrolimus group had to be switched to cyclosporine A. There was a trend toward more infections (0.7 ± 0.36 vs 0.55 ± 0.31, $P = .059$) in the cyclosporine A group. New-onset diabetes mellitus was observed in the tacrolimus group only (11% vs 0%, $P = .151$), whereas there was a higher incidence of hypertension (60% vs 11%, $P = .03$) in the cyclosporine A group.

Conclusion: This 2-center, prospective randomized study showed high immunosuppressive potency of both cyclosporine A and tacrolimus in combination with mycophenolate mofetil. No significant difference in incidence of acute rejection was observed between the 2 groups. Moreover, survival and incidence of infection were similar. Incidence of drug-related adverse events were similar, yet their spectrum was different.

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Although lung transplantation has become an established therapeutic option for the treatment of end-stage pulmonary disease, the long-term outcome is still limited by bronchiolitis obliterans (BO). The frequency and severity of acute rejection episodes are the most important risk factors for the subsequent development of BO. The standard immunosuppressive regimen, consisting of cyclosporine (INN: ciclosporin) A (CsA), azathioprine, and prednisolone, is associated with an unacceptably high incidence of BO. The use of new immunosuppressive drugs is expected to improve long-term results after lung transplantation.

Several groups have demonstrated that mycophenolate mofetil (MMF) decreases the incidence of acute rejection after lung transplantation.[1-3] For this reason, MMF has replaced azathioprine as standard immunosuppression in many centers. Lower rates of acute rejection and BO with the use of tacrolimus have been shown in a prospective randomized trial by Keenan and colleagues.[4] However, only one study, conducted in a small number of patients, has investigated the potential beneficial effect of a combination of tacrolimus and MMF and has reported an even lower rate of rejection.[5]

The aim of this 2-center, prospective randomized trial was to compare the efficacy and safety of a combination of tacrolimus, MMF, and prednisone versus a combination of CsA, MMF, and prednisone for prevention of acute rejection in lung transplantation.

TABLE 1. Comparison of CsA/MMF/steroids versus tacrolimus/MMF/steroids after lung transplantations: Demographics

	CsA	Tacrolimus	*P* value
Age (y)			
Mean ± SEM	46 ± 13	50 ± 10	.808
Range	20-66	24-65	NS
Sex (male/female)	15/22	22/15	.495
Underlying disease			
Emphysema	15 (41%)	22 (59%)	.495
Restrictive disease*	14 (38%)	10 (27%)	.635
Vascular disease†	5 (13%)	2 (6%)	.491
Cystic fibrosis	3 (8%)	3 (8%)	.671
Type of transplant procedure			
SLTX[3]	12 (32%)	16 (43%)	.673
BLTX[4]	25 (68%)	21 (57%)	.783
CMV D+/R−‡	9 (24%)	8 (24%)	.960

SLTX, Unilateral lung transplantation; *BLTX,* sequential bilateral lung transplantation.

*Restrictive disease: *CsA group,* idiopathic pulmonary fibrosis (n = 12), BO (n = 1), lymphangioleiomyomatosis (n = 1); *tacrolimus group*, idiopathic pulmonary fibrosis (n = 9), sarcoidosis (n = 1).

†Vascular disease : *CsA group,* primary pulmonary hypertension (n = 3), Eisenmenger disease (n = 2); *tacrolimus group,* primary pulmonary hypertension (n = 2).

‡CMV *mismatch,* An organ from a donor positive for CMV was transplanted into a recipient negative for CMV. Brackets contain percentages of the total number of patients in either of the study groups.

Patients and Methods

Patient Population and Study Design

Seventy-four consecutive adult patients undergoing primary lung transplantation between September 1997 and April 1999 were included in the study. Patients were randomized to receive either CsA (n = 37) or tacrolimus (n = 37) as part of their maintenance immunosuppression. Because of the higher risk for infectious complications, randomization was performed to evenly distribute patients with cytomegalovirus (CMV) mismatch (donor ± recipient), cystic fibrosis, or both among both groups. Formal approval for the conduct of this study was obtained from local ethics committees before enrollment, and informed consent was received from each patient. The trial was performed in accordance with the Declaration of Helsinki.

Patient demographics are shown in Table 1. There were no differences between the 2 groups regarding age, sex, type of procedure, and indication for transplantation.

Mean follow-up was 507 ± 258 days (range, 365-838 days) in the CsA group and 508 ± 248 days (range, 365-910 days) in the tacrolimus group.

Immunosuppression

Antithymocyte globulin induction. All patients received rabbit antithymocyte globulin (ATG) as induction treatment over the first 3 days after transplantation (thymoglobulin, 2.5 $mg \cdot kg^{-1} \cdot d^{-1}$; IMTIX-SangStat, Lyon, France).

Cyclosporine A. CsA was started intravenously at a dosage of 1 $mg \cdot kd^{-1} \cdot d^{-1}$ immediately after transplantation. Patients were switched to CsA capsules (Neoral) as early as possible after extubation. Target levels were between 250 and 350 ng/mL (FPIA) during the first month and around 200 ng/mL thereafter, depending on kidney function.

Tacrolimus. Patients in the tacrolimus group were started on tacrolimus intravenously at a dose of 0.015 mg/kg immediately after transplantation. Oral tacrolimus was administered at a dosage of 0.1 to 0.3 $mg \cdot kg^{-1} \cdot d^{-1}$ after extubation. Target levels were between 12 and 15 ng/mL during the first month and between 9 and 12 ng/mL thereafter, depending on kidney function.

Mycophenolate mofetil. MMF was administered at a dosage of 2 g/d. As long as patients were intubated, MMF was administered through a nasogastric tube and orally after extubation. Drug dose was reduced, or the drug was temporarily discontinued whenever adverse events (leukopenia and nausea) occurred.

Steroids. Methylprednisolone (500-1000 mg administered intravenously) was given before opening of the pulmonary arterial clamp. During the first 24 hours after transplantation, patients received 3 further doses of methylprednisolone (125 mg). On the first postoperative day, prednisone was started at 1 mg/kg and tapered to 0.5 mg/kg during the first week after transplantation. Prednisone was further tapered to 0.15 to 0.2 mg/kg within the first 3 months after transplantation.

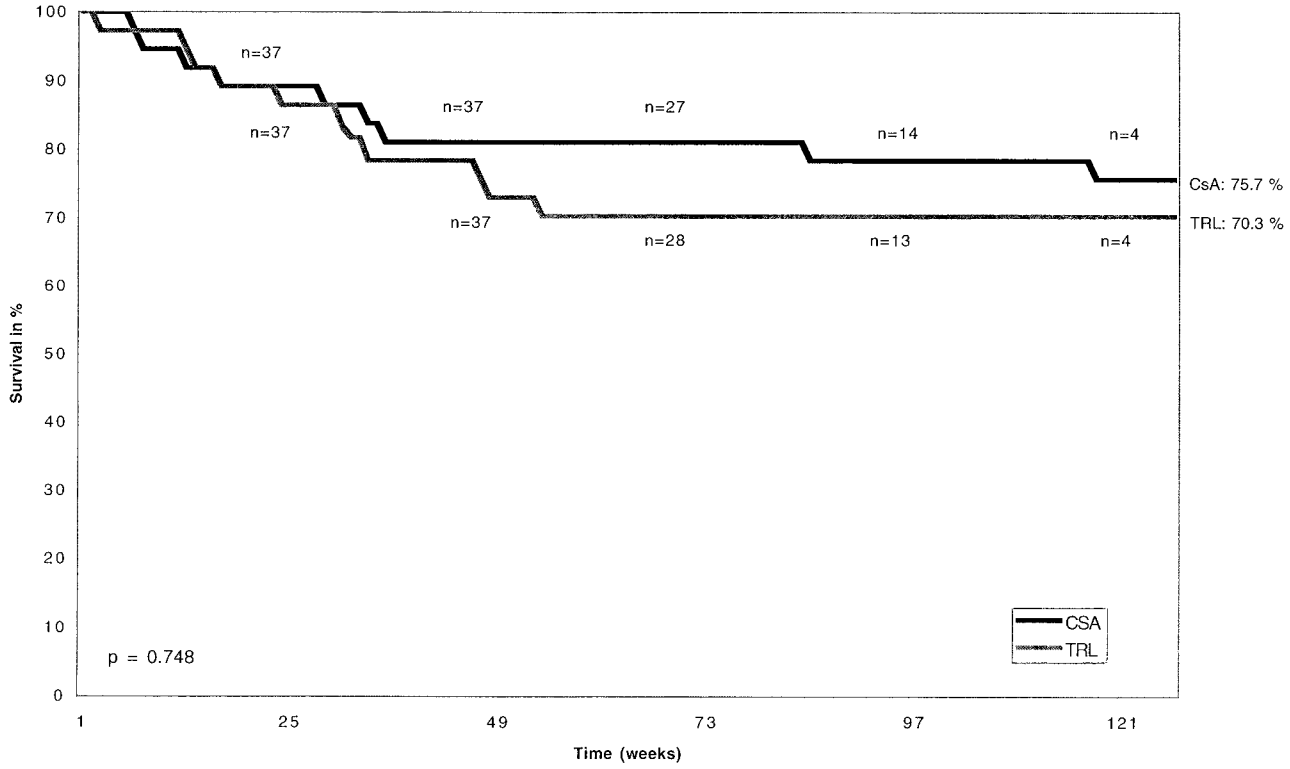

Figure 1. Kaplan-Meier estimated survival for patients with tacrolimus *(TRL)* or cyclosporine *(CsA)*. Numbers of patients at risk are shown along the curves.

Diagnosis and Treatment of Rejection

Diagnosis of acute allograft rejection was made on the basis of clinical (dyspnea, weakness, low-grade fever, and malaise), spirometric (sudden significant decrease in forced expiratory volume in 1 second, mean maximal expiratory flow, or both), and radiologic (perihilar or diffuse alveolar infiltrates) criteria when infection could be ruled out as a cause for these symptoms. Efforts were made to obtain transbronchial biopsy specimens for histologic diagnosis whenever a rejection episode was suspected. Surveillance transbronchial biopsies were performed at 3 weeks and at 3, 6, and 12 months after transplantation and graded according to the guidelines of the International Society for Heart and Lung Transplantation.[6,7]

Treatment of acute rejection was initiated if clinical, spirometric, or radiologic signs or symptoms were present (irrespective of histologic grade) or if histologic examination revealed acute rejection of grade A_2 or higher (irrespective of clinical findings).

Acute rejection episodes were treated with 500 to 1000 mg of intravenous methylprednisolone for 3 consecutive days, followed by an oral taper of steroids. The primary choice for treatment of ongoing or recurrent rejection was a switch from one study drug to another (CsA to tacrolimus or tacrolimus to CsA). If rejection persisted after a switch, a 10-day course of OKT3 (5 mg/d) was initiated.

Infectious Prophylaxis

Antibacterial prophylaxis consisted of piperacillin-tazobactam (4.5 g administered intravenously 3 times per day) for 10 days after transplantation. In case of positive bacterial cultures, antibiotic therapy was adjusted according to sensitivity tests. Antifungal prophylaxis consisted of aerosolized amphotericin B, which was administered until surveillance bronchoscopy demonstrated complete healing of the bronchial anastomosis. All patients received antiviral prophylaxis consisting of 10 mg $\cdot$ $kg^{-1} \cdot d^{-1}$ ganciclovir administered intravenously for 3 weeks, followed by 3 g/d orally until postoperative day 90. Additionally, patients received a course of anti-CMV hyperimmunoglobulin (Cytotect, 100 mL; Biotest, Dreireich, Germany) administered at days 1, 7, 14, 21, and 28 after transplantation. All patients received lifelong prophylaxis against *Pneumocystis carinii* and *Toxoplasma gondi* (trimetoprim-sulfamethoxazol 3 times per week).

Infectious Diagnosis and Treatment

Bacterial and fungal cultures were taken from donor and recipient bronchus. During any hospitalization, bacterial and fungal cultures were obtained from blood, urine, and sputum on a weekly basis, as well as from every bronchoalveolar lavage fluid specimen. CMV screening was performed by means of weekly measurement of CMV serology and detection of CMV early antigen in blood, urine, throat wash, and bronchoalveolar lavage fluid. Bacterial and fungal cultures, as well as polymerase chain reactions, for *Toxoplasma gondii* and *Pneumocystis carinii* were performed with each bronchoalveolar lavage. In addition, transbronchial biopsy specimens were histologically screened for CMV, bacterial, or invasive fungal infection.

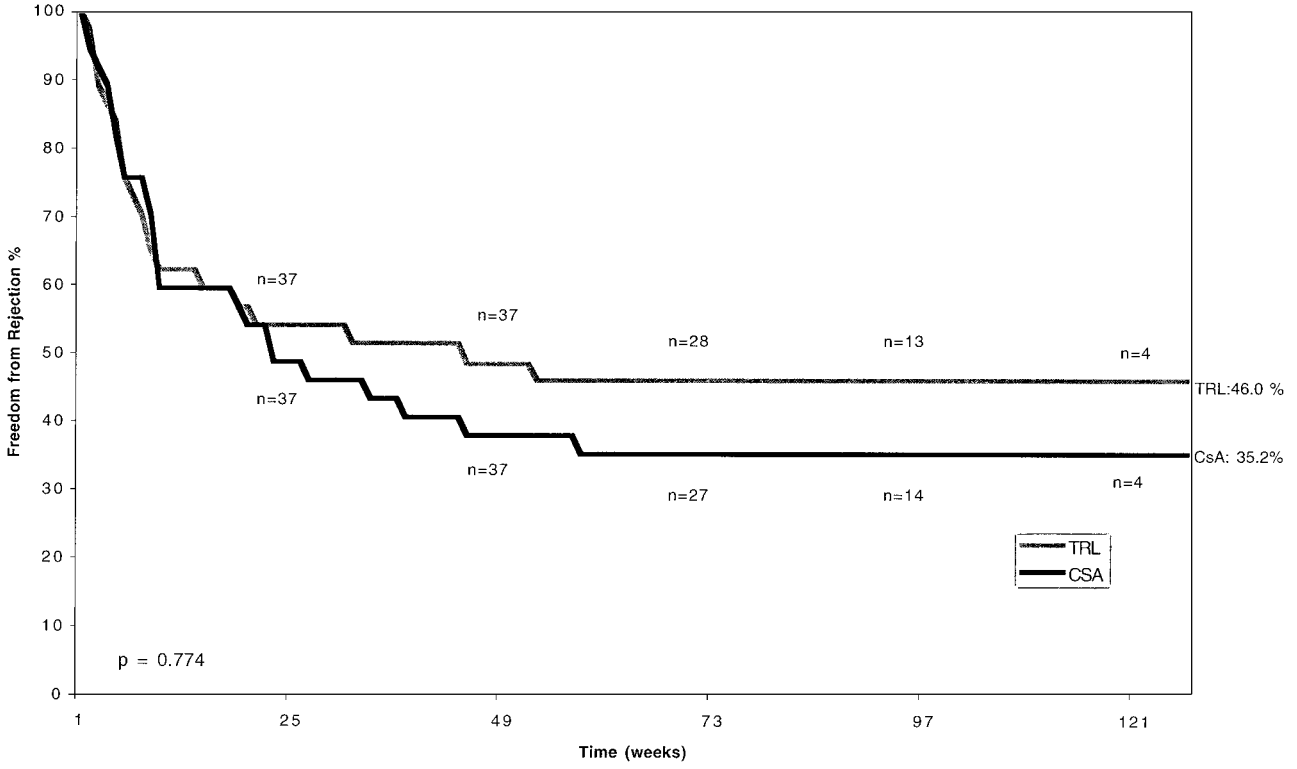

Figure 2. Kaplan-Meier estimated freedom from acute clinical rejection for patients with tacrolimus *(TRL)* or cyclosporine *(CsA)*. Numbers of patients at risk are shown along the curves.

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Bacterial and fungal infection was diagnosed, and treatment was initiated in the early postoperative phase when cultures were positive for microorganisms. In stable patients antibacterial and antifungal treatment was initiated in the eventuality of positive cultures when clinical symptoms were also present.

Therapy with intravenous ganciclovir was initiated when CMV early antigen was detected in blood or if CMV syndrome could be diagnosed and CMV was shed in urine, throat wash, or bronchoalveolar lavage fluid.

Bronchiolitis Obliterans Syndrome

BO was defined according to the guidelines of the International Society for Heart and Lung Transplantation.[8]

Study End Points

The primary end point of the study was the prevention of acute allograft rejection expressed as freedom from rejection and incidence of rejection episodes per 100 patient days. Secondary end points were survival, incidence of infectious episodes, and adverse events.

Patients were excluded from further analysis if they were switched from one study drug to the other or had to undergo retransplantation. Nevertheless, these patients were followed up and analyzed separately.

Statistical Analysis

Actuarial survival and freedom from rejection were calculated by using the Kaplan-Meier estimator and compared by means of log-rank testing. Episodes of rejection and infection were expressed per 100 patient-days and compared with the unpaired Student t test. Differences in proportions between the CsA and tacrolimus groups were calculated by using the χ^2 test.

Results

Survival

Three-, 6-, and 12-month survivals were 89%, 89%, and 82% in the CsA group compared with 89%, 84%, and 71% in the tacrolimus group (P = not significant, Figure 1). Causes of death were septic multiorgan failure (n = 4), bacterial pneumonia (n = 2), fungal infection (n = 1), and esophageal carcinoma (n = 1) in the CsA group compared with septic multiorgan failure (n = 5), fungal infections (n = 3), intracerebral mass bleeding (n = 1), CMV pneumonitis (n = 1), and tuberculosis (n = 1) in the tacrolimus group, respectively.

Two patients in the CsA group had to have a second transplant operation 22 and 50 days after the primary procedure because of unspecific graft failure. One of them died of bacterial pneumonia 1 month after retransplantation.

Acute Rejection

Freedom from acute rejection at 3, 6, and 12 months after transplantation was similar in both groups (60%, 46%, and 35% in the CsA group compared with 60%, 51%, and 46%

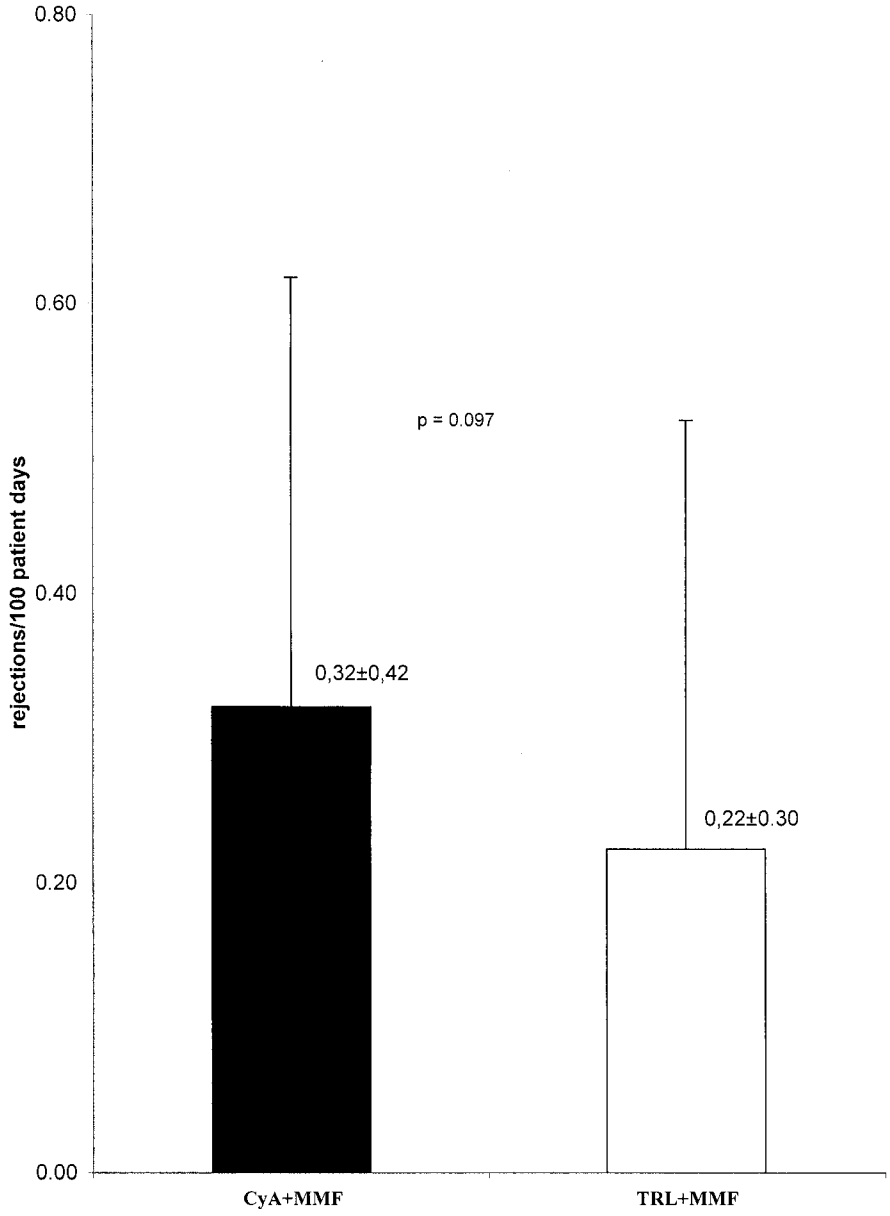

Figure 3. Acute clinical rejections per 100 patient-days. Comparison between patients treated with tacrolimus *(TRL)* and those treated with cyclosporine *(CyA). MMF,* Mycophenolate mofetil.

in the tacrolimus group, respectively; $P = .774$; Figure 2). The average number of acute rejection episodes per 100 patient-days was similar in both groups (tacrolimus group: 0.22 ± 0.30 vs CsA group: 0.32 ± 0.42; $P = .11$; Figure 3).

Recurrent Acute and Ongoing Rejection

Freedom from recurrent acute rejection episodes was not different between the 2 groups (CsA group: 87% vs tacrolimus group: 84%; $P = .967$) during the entire follow-up (Figure 4).

Four patients from the CsA group were switched to tacrolimus because of recurrent acute rejection episodes (months 4, 6, 7, and 11); of these, 3 patients survived without further evidence of acute rejection and without development of BO. The fourth patient, who was already in BO syndrome grade IIIb before the switch, died 10 months later. No patient from the tacrolimus group was switched to CsA.

Ongoing steroid refractory rejection was diagnosed in 3 patients in the CsA group and in 1 patient in the tacrolimus group and was treated with OKT3.

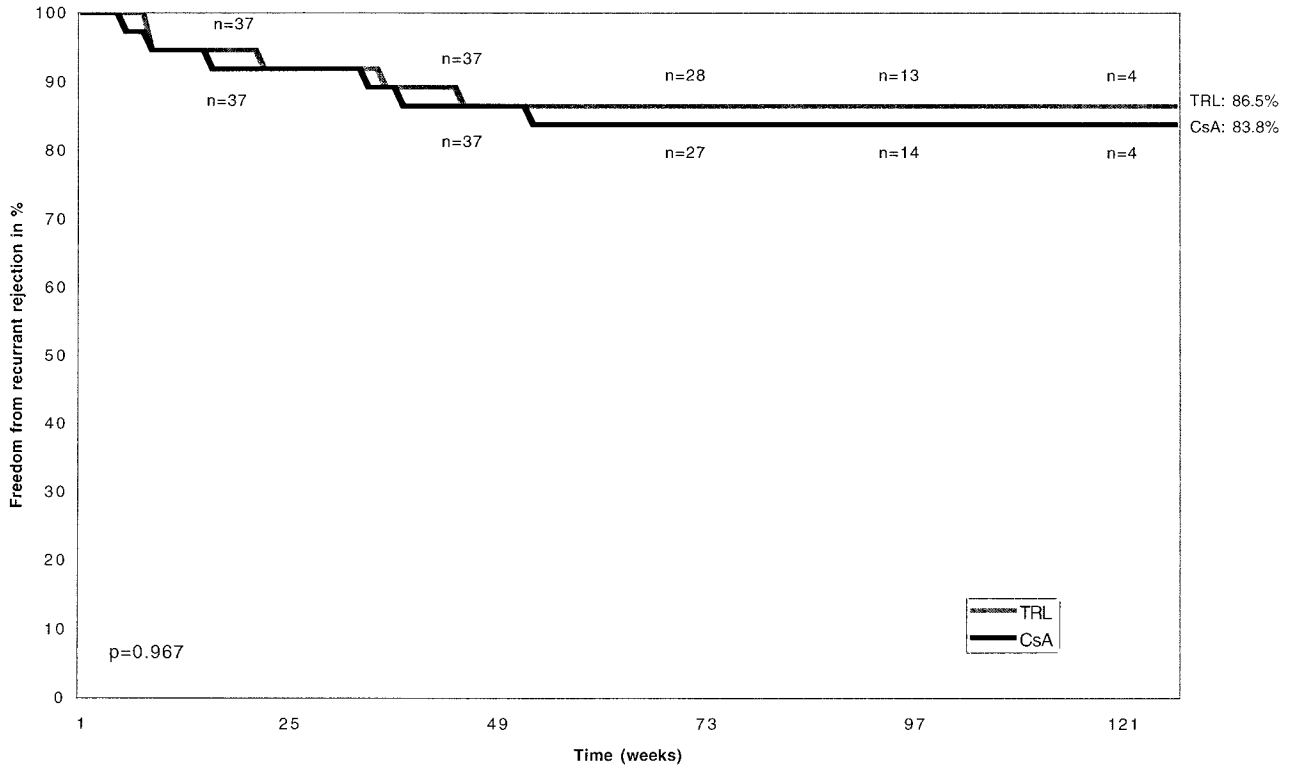

Figure 4. Kaplan-Meier estimated freedom from recurrent acute clinical rejection for patients with tacrolimus *(TRL)* or cyclosporine *(CsA).* Numbers of patients at risk are shown along the curves.

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Bronchiolitis Obliterans

Three patients in each group had BO syndrome during follow-up (BO syndrome grade IIIb, n = 2 in each group; and BO syndrome grade Ib, n = 1 in each group). One patient in each group had BO syndrome after recurrent acute rejection episodes. Two other patients (one in each group) had BO syndrome after late rejections, which were associated with noncompliance to study medication (Figure 5).

Infections

A trend toward a higher number of overall infection episodes per 100 patient-days was observed in the CsA group (CsA, 0.7 ± 0.36; tacrolimus, 0.55 ± 0.31; $P = .059$). There was also a trend toward higher rates of bacterial infections in the CsA group (0.44 ± 0.53) compared with that in the tacrolimus group (0.25 ± 0.35, $P = .089$), whereas incidence of fungal (tacrolimus group: 0.14 ± 0.32 vs CsA group: 0.09 ± 0.27; $P = .470$) and viral (CsA group: 0.18 ± 0.29 vs tacrolimus group: 0.16 ± 0.27; $P = .760$) infection was comparable between both groups (Figure 6).

Adverse Events

Adverse events data are shown in Table 2. At 6 and 12 months after transplantation, creatinine levels were similar in both groups. No patient from the tacrolimus group had renal insufficiency during intravenous administration of this drug. The percentage of patients with renal dysfunction (creatinine, >2.0 mg/dL) increased in both groups from month 6 to month 12 after transplantation.

The number of patients requiring antihypertensive treatment was significantly higher in the CsA group than in the tacrolimus group at 6 and 12 months, respectively ($P = .03$), whereas the need for statin therapy was similar in both groups ($P = .474$).

New onset of diabetes mellitus was observed only in the tacrolimus group (11% of patients at both 6 and 12 months, $P = .151$). Leukopenic events occurred in 7 (19%) patients in the CsA group compared with 8 (22%) patients ($P = .962$) in the tacrolimus group. In case of leukopenic events, MMF was reduced or discontinued temporarily. Incidence of gastrointestinal side effects (mostly nausea and diarrhea) was similar in both groups (CsA, n = 6; tacrolimus, n = 6). Two cases of malignant disease (posttransplant lymphoproliferative disease, n = 1; esophageal carcinoma, n = 1) developed in the CsA group 9 and 17 months after transplantation. No malignancies were observed in the tacrolimus group.

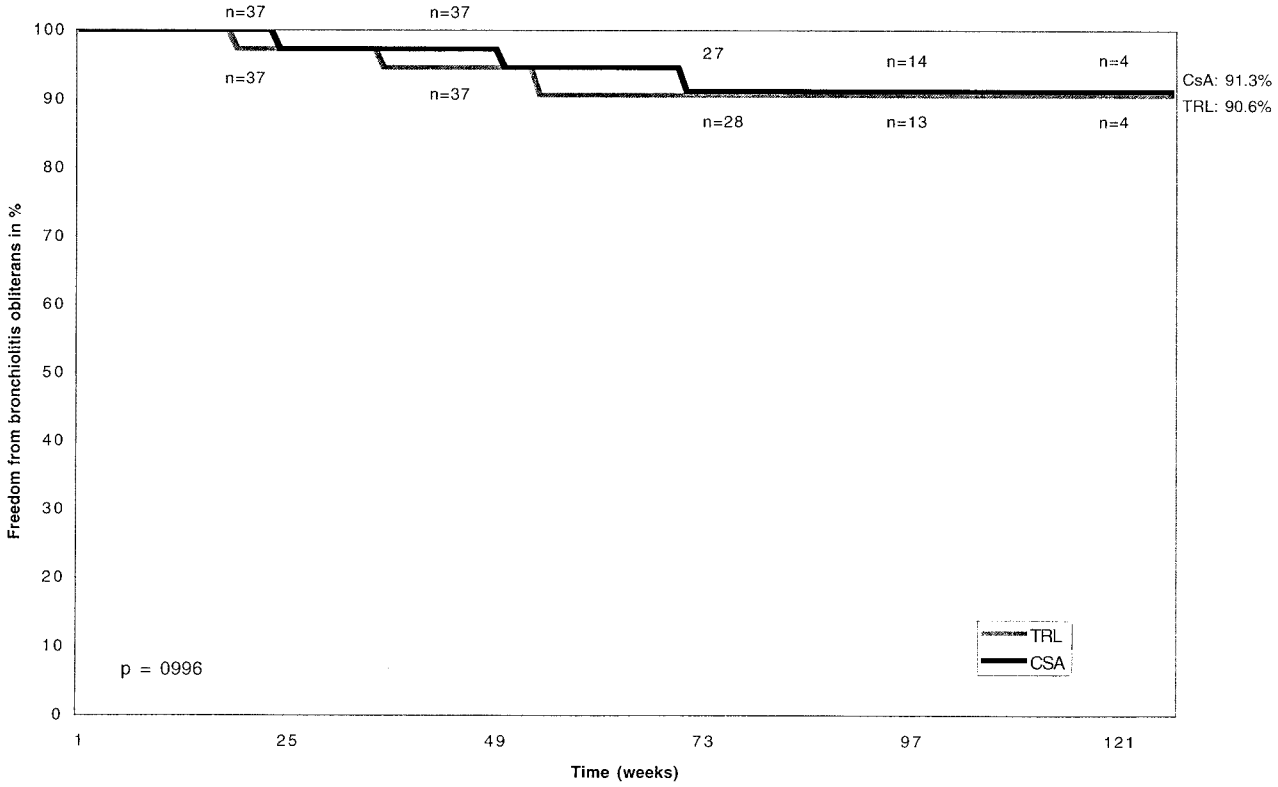

Figure 5. Kaplan-Meier estimated freedom from bronchiolitis obliterans for patients with tacrolimus *(TRL)* or cyclosporine *(CsA).* Numbers of patients at risk are shown along the curves.

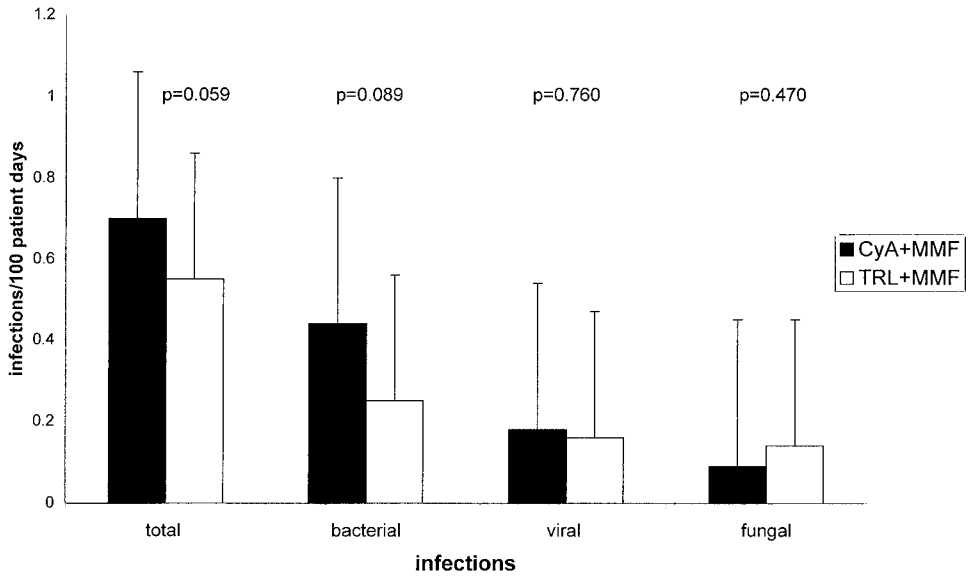

Figure 6. Overall, bacterial, viral, and fungal infections per 100 patient-days. Comparison between patients treated with tacrolimus *(TRL)* and those treated with cyclosporine *(CyA). MMF,* Mycophenolate mofetil.

TABLE 2. Adverse events at 6 and 12 months after lung transplantation in patients receiving either CsA/MMF/steroids or tacrolimus/MMF/steroids

	CsA	Tacrolimus	*P* value
Creatinine (mg/dL)			
6 mo (means ± SD)	1.4 ± 0.3	1.4 ± 0.4	1.000
12 mo (means ± SD)	1.5 ± 0.4	1.6 ± 0.7	.453
Renal dysfunction (creatinine >2.0)			
6 mo	3%	5%	.982
12 mo	10%	16%	.797
Patients receiving antihypertensive therapy (%)			
6 mo	41%	14%	.08
12 mo	60%	11%	.03
Patients treated for hypercholesterolemia (%)			
6 mo	41%	27%	.526
12 mo	75%	53%	.474
Diabetes mellitus (new onset)			
6 mo	0%	11%	.151
12 mo	0%	11%	.151
Malignancy at 12 mo (%)	5%	0%	.497
No. of overall adverse events per patient at 12 mo after transplantation	1.5 ± 0.9	0.9 ± 0.8	.097

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Discussion

This 2-center, prospective randomized study showed high immunosuppressive potency of both CsA and tacrolimus in combination with MMF. No significant difference in the incidence of acute rejection was observed between the 2 groups, yet there was a trend toward fewer rejections per 100 patient-days in the tacrolimus-MMF group. Survival and overall incidence of infection were similar. Only overall drug-related adverse events were different between the 2 groups.

Different protocols with new immunosuppressive drugs have been shown to decrease the incidence of acute rejection after lung transplantation. Studies by the Pittsburgh and Munich groups showed a lower rejection incidence when tacrolimus was used instead of CsA.[1,7] On the other hand, our group, as well as others, have shown that replacing azathioprine with MMF in combination with CsA decreased the incidence of acute rejection.[1-3] However, the only reported experience with a combination of tacrolimus and MMF derives from a small group of 12 patients.[7] The assumption that a combination of tacrolimus and MMF might have a different immunosuppressive potency than the combination of CsA and MMF derives from data that suggest a different influence of either tacrolimus or CsA on mycophenolate acid bioavailability. Studies at our centers are underway to detect the influence of these calcineurin inhibitors on mycophenolate acid blood levels.

No significant difference in the incidence of acute rejection between groups was observed. This observation is in contrast to a study performed by the Pittsburgh group that showed significantly lower rejection rates with tacrolimus compared with CsA. A potential explanation could be the use of CsA capsules (Neoral) instead of conventional CsA in our study. Yet it remains speculative whether the immunosuppressive potency of both combinations is equal or whether a difference did not become obvious only because of the limitations of this study. Limiting factors might be the overall small patient number and the study design itself. Although differences with regard to the type of procedure (unilateral lung transplantation vs sequential bilateral lung transplantation) and indications for transplantation were not significant, larger multi-institutional studies should be stratified for these variables to strengthen results.

A potential limiting factor for the interpretation of data with regard to acute rejection is the overall small number of patients. However, an important finding of this trial is the lower rejection rate in both groups compared with that seen in studies using tacrolimus or CsA in combination with azathioprine. Therefore, one could assume that the combination of either study drug with MMF instead of azathioprine is responsible for the lower rejection rate. The overall lower rate of rejection compared with that seen in other trials might be due to the use of ATG induction therapy. This assumption is supported by the results of a European multicenter tacrolimus heart pilot study, which showed significantly fewer rejection episodes in both study groups (CsA and tacrolimus) when ATG induction therapy was used compared with episodes in both groups without induction therapy.[9] However, no compelling data from randomized trials about the potential effect of ATG induction in lung transplantation are available thus far.

Acute rejection episodes are the strongest known risk factor for the development of chronic rejection, pathohistologically defined as BO.[10-14] BO, on the other hand, is the

most significant long-term cause of morbidity and mortality after lung transplantation.

Currently, follow-up of both study groups is too short to detect an effect on the incidence of BO. However, the low rejection rates in both groups are promising for long-term follow-up.

There is some evidence that the immunosuppressive potency of the tacrolimus-MMF combination might be higher than that of the CsA-MMF combination, probably because of pharmacokinetic interactions. Our experience with 4 patients switched from CsA to tacrolimus after recurrent acute rejection episodes is in accordance with those of others who showed similar experiences with tacrolimus rescue therapy.[15-18] During tacrolimus-MMF therapy (after switching), no acute rejection episodes were observed in these patients. There is too little knowledge on the long-term outcomes of such patients, and more studies have to be undertaken to gain information on the risk/benefit ratio of this therapeutic option.

Analysis of infectious complications showed a trend toward more overall and bacterial infections in the CsA group. Overall incidence of infections was similar to that reported with other immunosuppressive regimens.[1-5] Only the fact that there were 3 deaths from fungal infection in the tacrolimus group is worrisome. This points out that perhaps the combination of tacrolimus and MMF might increase the risk for severe fungal infections, and intensified prophylaxis should be warranted.

As expected, the spectrum of side effects was different according to the calcineurin inhibitor that was used. New onset of diabetes mellitus was seen only in the tacrolimus group. All patients had diabetes within the first 6 months after transplantation, and all of them remained insulin dependent, even after reduction of the tacrolimus dose. In our study there was a significantly lower rate of patients requiring antihypertensive therapy in the tacrolimus group, which is similar to data obtained by Taylor and colleagues in cardiac transplantation,[19] whereas there was no significant differences in terms of lipid disorders. Results of other studies regarding hyperlipidemia and hypertension are controversial.[4,9,19,20] Therefore patients treated with tacrolimus might have a lower cardiovascular risk unless they have diabetes.[21] The mechanisms for these differences are still not clear. The rate of renal dysfunction was similarly low in both groups and comparable with that seen in other studies.

Some transient phases of leukopenia were seen in both patient groups, especially in the presence of ATG and ganciclovir in the early postoperative course. Because the latter 2 agents have known leukopenic effects, leukopenia was not clearly attributable to MMF alone. In all patients, MMF dosage was reduced, or the drug was temporarily discontinued until leukocyte counts increased to normal levels. In none of the patients did MMF have to be discontinued permanently.

Summarizing this study, we show that both combinations (CsA-MMF and tacrolimus-MMF) have a high immunosuppressive potency, which results in comparable low acute rejection rates. Tacrolimus-MMF might be beneficial for immunologically high-risk patients, who are more prone to rejection episodes (ie, highly sensitized patients with positive cross-match) or for patients with a higher cardiovascular risk. On the other hand, CsA might be used preferentially in diabetic patients or patients with a risk for diabetes (eg, patients with cystic fibrosis).

At present, the question of which of these drug combinations offers better immunosuppression can not be answered and therefore must remain a center-specific decision.

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