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ORIGINAL ARTICLE

Tacrolimus and mycophenolate mofetil as first line immunosuppression after lung transplantation

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Summary

The optimal maintenance therapy after lung transplantation remains to be established. The aim of this study was to analyse the impact of tacrolimus and mycophenolate mofetil (MMF) as first line immunosuppression on long-term survival and Bronchiolitis Obliterans Syndrome (BOS). From January 1996 through December 2006, all 155 recipients receiving tacrolimus and MMF as maintenance immunosuppression were included in this study. Tacrolimus and MMF was discontinued in 36 patients (23.2%). The overall survival rates were 91.6% at 6 months, 86.4% at 1 year, 74.9% at 3 years, 60.3% at 5 years and 32.4% at 10 years. The overall freedom from acute rejection was 74.6%, 63.2% and 59.4% at 1, 3, and 5 years respectively. The overall BOS-free survival was 95.6% at 1 year, 88.4% at 3 years, 69.5% at 5 years and 30.5% at 10 years. The development of BOS ≥ 1 was associated with a significantly increased risk of death and reduced long-term survival. The combination of tacrolimus and MMF offers safe and reliable maintenance immunosuppression after lung transplantation. However, substantial improvements of long-term survival and freedom from BOS might only be achieved by a change in organ allocation policies and patient management beyond differential immunosuppressive protocols.

Introduction

Within the past two decades, lung transplantation (LTx) has become a therapeutic option for patients with end-stage lung disease [1]. However, survival rates are still limited compared with those achieved after transplantation of other solid organs. Although, there was improvement in survival in successive eras, it has been concentrated in the first year after LTx. These data suggest that management strategies have been more successful in reducing early fatal complications than in diminishing potentially lethal long-term damage to the graft [2]. Infections and Bronchiolitis Obliterans Syndrome (BOS) remain the leading causes of death. Both complications are a sign of inadequate immunosuppression and optimization of the regimen might be crucial for improving the long-term outcome [3]. The conventional approach consisted of cyclosporine, azathioprine and corticosteroids, with or without the use of cytolytic agents. Despite this regimen, acute allograft rejection, which is a major risk factor for the development of BOS, frequently occurs after LTx [4]. Based upon reports that the incidence of acute rejection (AR) after kidney, liver and heart transplantation can be reduced by tacrolimus and mycophenolate mofetil (MMF), an increasing number

of LTx patients are treated with these drugs. A controlled trial by Keenan *et al.* [5] demonstrated a strong trend towards the reduction of the incidence of AR and BOS with the use of tacrolimus as compared with cyclosporine both in combination with azathioprine. More recently this important finding was confirmed in another randomized study [6]. Several small retrospective observations suggested that MMF is a promising alternative to azathioprine, associated with a lower rate of allograft rejection [7,8]. However, in a controlled trial, overall rejection rates and survival at 6 months after LTx were similar for cyclosporine in combination with either MMF or azathioprine [9].

The International Society for Heart and Lung Transplantation (ISHLT) registry data indicate that currently tacrolimus is the dominant calcineurin inhibitor, and MMF is the main purine synthesis antagonist after LTx [2]. Nevertheless, data on the impact of a combination of tacrolimus and MMF on AR, BOS and survival in a long-term follow-up are not available. These drugs have become our standard immunosuppressive therapy since 1996 [10,11]. This report reviews more than 10 years of experience of the Munich Lung Transplant Program with tacrolimus and MMF with particular emphasis on long-term outcomes, infections and adverse events.

Methods

Patient population

From January 1996 through December 2006, all 155 LTx patients who received tacrolimus and MMF as primary immunosuppression were included. Follow-up data including demographic data, bronchoscopy results, laboratory values, pulmonary function test data, immunosuppressive protocol, survival status and cause of death were collected through October 1, 2007.

Standard care of lung transplant patients

Lung transplantation recipients included in this study received no induction therapy and were maintained on corticosteroids, tacrolimus and MMF. In case of recurrent AR, toxicity or BOS, a switch to an alternative immunosuppressive regimen based on a case-by-case decision was accomplished.

Tacrolimus was started intravenously at a dose of 0.015 mg/kg immediately after transplantation and switched to oral administration after extubation. Target trough levels were between 12 and 15 ng/ml during the first year and lowered to 9–12 ng/ml thereafter, depending on kidney function.

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

Corticosteroids: Methylprednisolone (500–1000 mg administered intravenously) was given before opening of the pulmonary arterial clamp. During the first 24 h, patients received three further doses of methylprednisolone (125 mg). On the first postoperative day, prednisolone was started at 1 mg/kg and tapered to 0.15–0.2 mg/kg within the first 3 months.

Donor positive/recipient-negative patients received oral CMV prophlyaxis with ganciclovir for a period of 3 months. In all other cases, a viral prophylaxis with acyclovir was administered for 3 months. In addition, preemptive therapy with ganciclovir and/or immunoglobulin was initiated based on positive CMV antigenemia.

Acute rejection and Bronchiolitis Obliterans Syndrome

During the first 3 months after transplantation, patients underwent at least two bronchoscopies with bronchoalveolar lavage (BAL) and transbronchial biopsy. Furthermore, clinically indicated bronchoscopies were conducted for new respiratory symptoms (e.g. shortness of breath, new radiographic findings, >10% decline from baseline forced expiratory volume in 1 s and hypoxemia). After the first 3 months, only the clinically indicated and follow-up bronchoscopies to monitor for treatment response were performed. AR was diagnosed according to the Lung Rejection Study Group criteria [12]. Grade of AR $\geq$ A2 was considered positive and treated with methylprednisolone at a dose of 500 mg/day for three consecutive days. In case of AR A = 1, decision to treat was based on clinical status. Isolated lymphocytic bronchitis was not treated. The diagnosis of BOS was established using the ISHLT definition [13].

Statistical analysis

Statistics were calculated using SPSS software version 15.0.2. for Windows (SPSS Inc., Chicago, IL, USA). The demographic data and outcomes between groups were compared using two-sided chi-squared test or two-sided Fisher's exact test (when expected cell size was less then 5) for categorical variables and two-tailed Student's *t*-tests of independent samples for continuous variables. Actuarial survival, freedom from acute rejection and BOS were calculated using the Kaplan–Meier Method and groups were compared by means of log-rank testing. To evaluate for an association between acute rejection, BOS and death univariate Cox regression analysis was used. Results were considered statistically significant at $P < 0.05$.

Results

One hundred fifty-five LTx recipients were included in this study. The mean duration of observation per patient was 3.54 ± 0.21 years (median 3.05, range 0.02–10.50) and the study included 549 patient-years of follow-up. The baseline characteristics are summarized in Table 1.

Airway stenoses

The proportion of patients experiencing significant airway stenoses requiring interventions was 18.1% (28 patients). In 19 cases dilation or LASER treatment and in eight cases stent placement were needed. In one case, stent dislocation occurred outside the hospital and the patient eventually died.

Discontinuation of immunosuppression

The initial therapy with tacrolimus and MMF was discontinued in 36 patients (23.2%) at an average time of 2.55 ± 0.32 years after transplantation (median 2.14, range 0.18–7.71). Tacrolimus was discontinued in seven patients (19.4%) at an average time of 2.69 ± 0.87 years (median 1.92, range 0.95–7.71) and MMF was stopped in 29 patients (80.6%) at an average time of 2.51 ± 0.35 years (median 2.35, range 0.18–7.29). Reasons for discontinuation are listed in Table 2 and details for outcome data and accomplished changes are given in the related sections.

Survival

The overall survival rates for the entire cohort of patients (n = 155) were 93.5% at 3 months, 91.6% at 6 months, 86.4% at 1 year, 74.9% at 3 years, 60.3% at 5 years, 52.0% at 7.5 years and 32.4% at 10 years (Fig. 1a). Survival half-life was 8.51 years for all patients and conditional half-life for the subset of recipients who were alive 30 days after transplantation was 8.87 years (n = 145) respectively. Among the group of patients with discontinuation of tacrolimus and MMF, survival half-life was reduced to 6.54 years with a trend for an increased risk of death (P = 0.07). However, the discontinuation of tacrolimus and MMF for reasons other than BOS or AR had no significant impact on survival and the half-life of this subset of patients was 8.51 years (n = 25). Survival rates for recipients maintained on tacrolimus and MMF throughout the study period (n = 119) were 92.4% at 3 months, 89.1% at 6 months, 84.0% at 1 year, 70.2% at 3 years, 61.6% at 5 years, 59.2% at 7.5 years respectively.

Table 1. Baseline characteristics (n = 155 patients).

Follow-up (years ± SEM)	3.54 ± 0.21
Female, *n* (%)	76 (49%)
Age (years ± SEM)	48.61 ± 0.94
Underlying Disease, *n* (%)	
COPD	42 (27.1%)
CF/Bronchiectasis	19 (12.3%)
IPF	42 (27.1%)
α_1-anti-trypsin deficiency emphysema	15 (9.7%)
Other	37 (23.8%)
Ischemic Time (min ± SEM)	338.6 ± 7.4
Type of Transplant, *n* (%)	
Single lung transplant	73 (47.1%)
Bilateral lung transplant	82 (52.9%)
CMV mismatch (donor+/recipient–)	28 (18.1%)

COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; IPF, idiopathic pulmonary fibrosis; CMV, cytomegalovirus; SEM, standard error of the mean.

Table 2. Reasons for discontinuation of Tacrolimus and mycophenolate mofetil (MMF).

	Discontinuation of	
Complication	Tacrolimus (n = 7)	MMF (n = 29)
BOS ≥ 1	3 (43%)	9 (31%)
Infection	1 (14%)	9 (31%)
Renal insufficiency	3 (43%)	2 (7%)
Diarrhea	0	4 (14%)
Leukopenia	0	3 (10%)
Cachexia	0	1 (3%)
Acute recurrent rejection	0	1 (3%)

BOS, Bronchiolitis Obliterans Syndrome.

Acute rejection and Bronchiolitis Obliterans Syndrome

An AR A ≥ 2 was detected in 35.4% (n = 55) of recipients. 72% of AR A ≥ 2 were diagnosed during the first 12 months at an average time of 0.84 years after transplantation (median 0.07, range 0.01–7.53). The overall freedom from AR A ≥ 2 was 74.6%, 63.2% and 59.4% at 1, 3, and 5 years respectively. AR was associated with a significantly reduced survival and increased risk of BOS ≥ 1 (survival: Hazard ratio (HR) = 2.54, 95% confidence interval (CI) 1.41–4.58, P = 0.02; BOS: HR = 3.85, 95% CI 1.88–7.85, P < 0.001, Figs 1b and 2b). Recipients developing BOS ≥ 1 showed a significantly elevated percentage of all grades of AR A and lymphocytic bronchitis grade B ≥ 2. However, in the BOS group a significantly increased number of bronchoscopies was performed (Table 3).

Bronchiolitis Obliterans Syndrome

Bronchiolitis Obliterans Syndrome ≥ 1 was diagnosed in 40 (28.6%) of 140 eligible recipients. Fifteen recipients

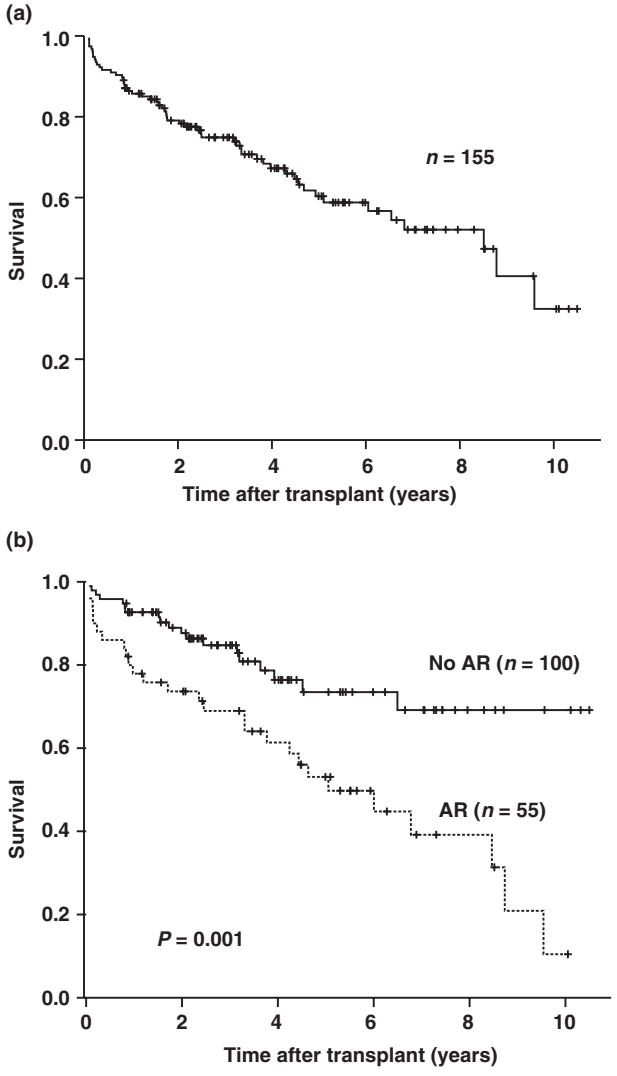

Figure 1 (a) Overall survival for all 155 recipients receiving tacrolimus and mycophenolate mofetil (MMF) as maintenance immunosuppression. (b) Survival after lung transplantation stratified by the presence (dashed line) or absence (solid line) of acute rejection episodes (AR) ≥ 2.

were ineligible for BOS classification as a result of a lack of sufficient follow-up data or large airway problems. Twenty-five percent of patients had developed BOS by 4.5 years and 50% by 7.3 years. The overall BOS-free survival was 95.6% at 1 year, 88.4% at 3 years, 69.5% at 5 years, 48.9% at 7.5 years and 30.5% at 10 years (Fig. 2a). BOS stage 1 was diagnosed in 18 cases (12.9%) at an average time of 3.08 years (mean 2.62, range 0.38–8.94), BOS stage 2 in 10 cases (7.1%) at an average time of 2.77 years (mean 1.84, range 0.63–8.04), BOS 3 in 12 cases (8.6%) at an average time of 3.54 years (mean 3.42, range 1.30–8.02). The development of BOS was associated with a significantly increased risk of reduced survival (HR = 4.50, 95% CI 2.32–8.74, $P < 0.001$, Fig. 3a).

The decision to treat BOS was made on case-to-case basis without any protocolized approach, based on the extent of functional decline, association with infection, clinical status, BOS stage and co-morbidities. Sirolimus was substituted for MMF (22.5%, $n = 9$) or tacrolimus (7.5%, $n = 3$) and in six recipients the anti-Interleukin-2Rα antibody daclizumab was administered [14].

Moreover, 13 patients received azithromycin with a stable course of respiratory function in four cases after onset of BOS. After conversion from MMF to sirolimus in one patient with recurrent acute rejection despite high-dose methylprednisolone, no more acute rejection episodes were detected. Nevertheless, this patient eventually developed BOS stage 1 with stabilization of functional deterioration only after initiation of azithromycin therapy. However, because of association with recurrent infections and poor clinical condition, seven (17.5%) patients were maintained on a single treatment regimen with tacrolimus despite development of BOS.

Pulmonary infections

The number of BAL results with positive cultures, staining or polymerase chain reaction (PCR) for relevant

Table 3. Distribution of survival, acute rejection and lymphocytic bronchitis between recipients with and without Bronchiolitis Obliterans Syndrome.

Distribution	NON BOS (n = 94)	BOS ≥ 1 (N = 40)	P value
Death, n (%)	12 (13%)	28 (70%)	<0.001*
Number of bronchoscopies (mean ± SEM)	2.89	5.08	<0.001*
Percentage of A1 episodes (n)	31% (29)	62.5% (25)	0.024*
Percentage of A2 episodes (n)	20% (19)	65% (26)	<0.001*
Percentage of A3 episodes (n)	0% (0)	12.5% (5)	<0.001*
Percentage of B1 episodes (n)	77% (73)	29% (73)	n.s.
Percentage of B2 episodes (n)	27% 25	60% 24	<0.001*
Percentage of B3 episodes (n)	9.6% 9	30% 12	0.003*

n.s., not significant. No patient in either group had an episode of A4 rejection or an episode of B4 lymphocytic bronchitis. *$P < 0.05$.

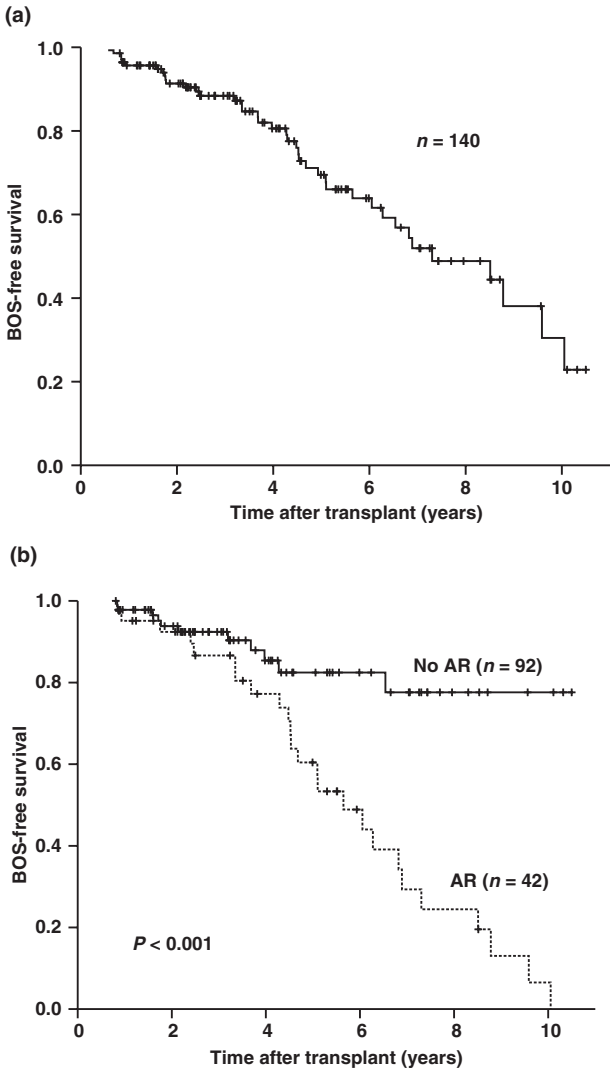

Figure 2 (a) Overall Bronchiolitis Obliterans Syndrome (BOS)-free survival of eligible patients (n = 140). (b) BOS-free survival after lung transplantation stratified by the presence (dashed line, n = 42) or absence (solid line, n = 92) of acute rejection episodes (AR) ≥ 2. Six patients (4.3%) were excluded from this analysis because of lacking or ambiguous histology before the onset of BOS.

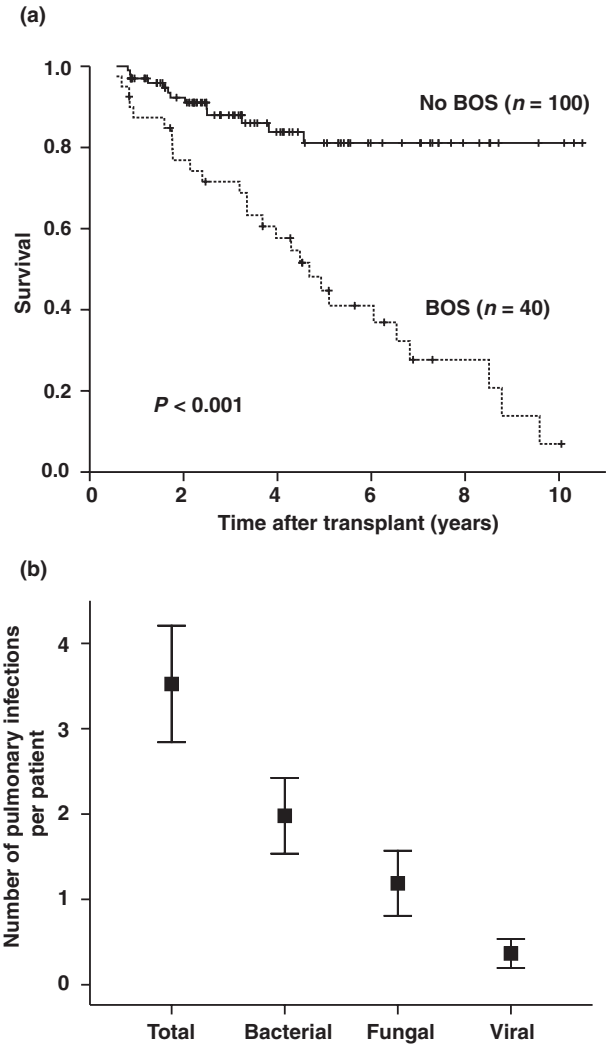

Figure 3 (a) Survival after lung transplantation stratified by the presence (dashed line) or absence (solid line) of Bronchiolitis Obliterans Syndrome (BOS). (b) Incidence of infectious pulmonary complications during the study period assessed by bronchoalveolar lavage with positive cultures, staining or polymerase chain reaction (PCR) for relevant bacterial, fungal or viral micro-organisms.

Table 4. Incidence of medical complications during the study period.

Complication	*n* (%)
New-onset diabetes mellitus	38 (26.6%)
Systemic hypertension	93 (65.0%)
Chronic kidney disease (>1.2 mg/dl)	91 (61.8%)
Creatinine 1.2–2.0 mg/dl	64 (43.2%)
Creatinine 2.0–3.0 mg/dl	16 (10.8%)
Creatinine >3.0 mg/dl	6 (4.1%)
Requiring chronic dialysis	5 (3.7%)

bacterial, fungal or viral micro-organisms is depicted in Fig. 3b. Bacterial and fungal infections were diagnosed and treatment was initiated in the early postoperative phase when cultures were positive or in case of functional deterioration. In stable patients, decision to treat was based on symptoms and clinical status. In 13 recipients, the main reasons for the permanent modification of immunosuppression were pulmonary infections (n = 10) and associated leukopenia (n = 3). Sirolimus was substituted for MMF in four patients. A conversion from tacrolimus to cyclosporine and from MMF to azathioprine was accomplished in only two cases. However, the majority of patients (n = 7) was maintained on a single immunosuppressive protocol with tacrolimus.

Table 5. Causes of death.

Cause of death	Overall *n* = 55 (%)	Time after transplant <12 months *n* = 22 (%)	Time after transplant >12 months *n* = 33 (%)
Technical complications	2 (3.6%)	0 (0%)	2 (6.1%)
Cardiovascular	5 (9.1%)	4 (18.2%)	1 (3.0%)
Infection			
Cytomegalovirus	1 (1.8%)	1 (4.5%)	0 (0%)
Non cytomegalovirus	12 (21.8%)	6 (27.3%)	6 (18.2%)
Acute rejection	3 (5.5%)	2 (9.1%)	1 (3.0%)
Bronchiolitis Obliterans Syndrome	17 (30.9%)	1 (4.5%)	16 (48.5%)
Graft failure	6 (10.9%)	6 (27.3%)	0 (0%)
Malignancy	5 (9.1%)	1 (4.5%)	4 (12.1%)
Others	4 (7.2%)	1 (4.5%)	3 (9.1%)

Medical complications

New-onset diabetes mellitus was observed in 38 patients (26.6%), 65% of recipients required antihypertensive treatment and 61.8% developed some stage of chronic kidney disease, respectively (Table 4). There was a significant association between the development of moderate to severe decrease in kidney function and the incidence of systemic hypertension ($P < 0.05$). Because of progressive renal failure, sirolimus was substituted for tacrolimus in three cases and for MMF in two patients. However, five (3.7%) lung transplant recipients eventually required chronic dialysis. Chronic diarrhea was attributed to MMF in four cases resulting in discontinuation. Sirolimus was substituted for MMF in one patient and a conversion to azathioprine was carried out in two recipients whereas one patient was maintained on tacrolimus monotherapy. In one case of otherwise intractable cachexia, azathioprine was substituted for MMF.

Causes of death and malignancies

Graft failure and non cytomegalovirus infection were the main cause of death during the first 12 months after transplantation. BOS, infections and malignancies became the predominant causes of death thereafter (Table 5). Overall, eleven (7.1%) recipients had some type of malignancy including skin cancer ($n = 3$), lymphoma ($n = 2$), lung carcinoma ($n = 3$), stomach cancer ($n = 1$), breast cancer ($n = 1$) and liver carcinoma ($n = 1$).

Discussion

Based on favorable results in several solid organ transplant programs, we shifted from the cyclosporine and azathioprine combination to tacrolimus and MMF beginning in 1996. To the best of our knowledge, this study is the first to define the long-term results of the combination of these drugs as primary maintenance therapy after LTx.

The Munich Lung Transplant Program demographics and transplantation procedures are in concordance with those reported previously. However, our distribution of diagnoses indicates a relatively high proportion of recipients with idiopathic pulmonary fibrosis (IPF) [2,15,16]. We speculate that this difference is partially explained by the role of our institution as an important referral center for IPF patients for the purpose of clinical trials and different patient selection criteria.

The overall survival rates in our series are consistently higher than those numbers reported by the ISHLT database. However, our data are not superior to the long-term results of other high-volume transplant institutions with cyclosporine and azathioprine based maintenance regimen [2,15–17].

Because of differences in demography, transplant procedure, standard care, era effect, and patient selection, inter-center comparisons should be interpreted cautiously. Nevertheless, our analysis demonstrates a remarkably low incidence of BOS and an excellent overall BOS-free survival. ISHLT data show a time period of only 5.6 years until 50% of patients developed BOS. By contrast, the respective interval for our patients was 7.3 years [2]. The University of Stanford reported a relatively high incidence of BOS with an overall freedom from BOS of 84%, 64% and 40% at 1, 3, and 5 years respectively. In this series from 1989 to 1999, all 127 patients received an induction therapy and a maintenance therapy with cyclosporine and azathioprine [16]. Burton *et al.* [18] reported a conditional BOS-free survival depending on BOS Grade within a range of 74.9% to 86.1% at 1 year, 48.4% to 65.8% at 3 years, 34.4% to 53.6% at 5 years and 12.6% to 31.7% at 10 years for total of 389 transplant patients from 1992 to 2004 with a cyclosporine and azathioprine based regimen.

As well documented in the literature, we found a close association between AR and an increased risk of BOS. Our observation of a reduced incidence of BOS using tacrolimus/MMF is in line with the relatively low number of AR detected in our program. We clearly recognize an important limitation of our protocol with respect to this conclusion. As we performed bronchoscopies beyond the first 3 months for clinical indications only, we might have missed asymptomatic AR episodes. In addition, symptomatic recipients were more likely to have bronchoscopies with the risk of a selection bias in favor of detecting AR in BOS patients. Nevertheless, according to ISHLT data, the combination of tacrolimus and MMF was associated with the lowest average number of AR episodes in the first year [2]. As shown by Hachem *et al.*, [6] tacrolimus was associated with a significantly reduced burden of AR and

lymphocytic bronchitis and a trend for a decreased incidence of BOS in comparison to cyclosporine when combined with azathioprine. Interestingly, the previous study of Keenan *et al.* [5] likewise comparing tacrolimus and cyclosporine combined with azathioprine, found no significant difference in AR episodes but a significantly greater freedom from obliterative bronchiolitis for tacrolimus. In contrast another multi-center study failed to produce any statistically significant difference in the number of patients experiencing AR and BOS at 3 years when receiving cyclosporine either in combination with MMF or azathioprine. Remarkably in this trial, the incidence of AR was as high as 60% and the freedom from BOS was only 74%, which compares unfavorably with our own data at 3 years. Moreover, the authors report a high rate of withdrawals (MMF group 46.5%, azathioprine group 59.6%) mainly because of lack of efficacy and adverse events [19].

Encouraged by retrospective data, two prospective trials comparing tacrolimus/MMF and cyclosporine/MMF were initiated including patients of the Munich Lung Transplant Program [20–22]. Taken together survival was similar in both groups with a strong trend toward increased incidence of BOS in the cyclosporine group [23,24]. Of note, in contrast to transplant recipients in our series, patients in these trials were subjected to induction therapy which may have obscured differences between the treatment arms.

Tacrolimus and cyclopsorine are known to increase the incidence of diabetes mellitus. However, the use of tacrolimus is associated with an additional increased risk compared with cyclosporine [25]. This adverse effect is reflected in the finding that more than a quarter of our patients developed new-onset diabetes mellitus. Furthermore, systemic hypertension, chronic kidney disease and to a lesser extent infections and malignancies are common complications in our transplant population with a frequency in line with previously published studies [2,6,10,19]. Because of the development of powerful immunosuppressants and a history of greater tobacco use in chronic obstructive pulmonary disease and IPF patients undergoing LTx, opportunistic infections including uncommon invasive fungi and advanced lung cancer stages contribute significantly to long-term mortality. Therefore, early detection strategies by yearly CT screening and a proper diagnostic approach including antifungal susceptibility testing should be considered for improving the otherwise poor prognosis [26,27]. In addition, rare complications after solid organ transplantation like acute graft-versus-host disease are presumably underdiagnosed in most lung transplant populations because of non specific clinical and histologic features [28].

Based on the assumption that tacrolimus and MMF offer a promising maintenance regimen after LTx, our more than 10-year experience demonstrates a high immunosuppressive potency for these drugs. The combination of tacrolimus and MMF is a safe and reliable alternative to cyclosporine and azathioprine with an excellent risk-benefit profile. The long-term results of this program compare favorably with international data and support the notion that in particular the use of tacrolimus as the initial calcineurin inhibitor may retard the development of BOS. However, our program did not achieve long-term survival rates superior to the best international centers and our retrospective study did not include an adequate control group. So far, BOS still presents as the most important single cause of death after LTx and this applies to our series as well. With AR as the most apparent risk factor, alloantigen-independent mechanisms including infections are increasingly considered as important contributors [4,29]. Therefore, improvement of outcome after LTx may not be achieved merely by variation of the immunosuppressive protocol. The impact of differential regimen may be underscored by the Swiss experience. Reporting excellent survival rates and an exceptionally low burden of BOS, the Swiss program uses cyclosporine, tacrolimus, MMF or azathioprine depending on individual factors but applies a comprehensive surveillance follow-up to every recipient [30]. Nevertheless a seemingly unavoidable fraction of patients develops AR, infections and BOS despite optimized care [17]. Fortunately, there is a significant percentage of recipients untouched by BOS with a stable course beyond 10 years. We speculate that a thorough evaluation of these long-term survivors will provide important insights into the factors determining the fate of the lung allograft. As the side-effects of long-term immunosuppressive therapy are sobering, new therapeutic approaches are needed to induce tolerance in the organ recipient. Efforts to minimize immunosuppression and new strategies established in animal transplant models like mixed chimerism combined with a non toxic conditioning regimen may provide a more successful balance between rejection and complications secondary to the use of non specific immunosuppressive agents [31]. Eventually, this might change organ allocation policies and long-term management beyond immunosuppressive therapy of lung transplant recipients.

Authorship

CN: wrote the paper. CN, PH, GZ, HL, RB, RH, LF, PU, IB, JB: collected data. PH, IB, JB, BR: analysed data. JB, BR: designed study.

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