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The value of switching from cyclosporine to tacrolimus in the treatment of refractory acute rejection and obliterative bronchiolitis after lung transplantation

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Abstract Standard cyclosporine-based immunosuppression is ineffective in the treatment of refractory acute rejection (RAR) and obliterative bronchiolitis (OB) that follows lung transplantation. The aim of this study was to evaluate the results of switching from cyclosporine to tacrolimus in the treatment of these situations. Nineteen patients entered the study. The indication for switching was OB in 11 patients and RAR in 8. Mean age was 41.3 ± 13.1 years. In patients with RAR, the number of acute rejections was 1.5 ● 0.7 and there were zero episodes per patient per 100 days before and after switching, respectively ($P = 0.02$). There was no significant reduction of the decline of forced expiratory volume (FEV_1) within 6 months after switching in patients with OB. We conclude that the conversion from cyclosporine to tacrolimus was associated with favourable results in the treatment of RAR. Further studies are required to assess the influence of this approach in the treatment of OB.

Keywords Lung transplantation · Immunosuppression · Tacrolimus · Acute rejection · Obliterative bronchiolitis

Introduction

Lung transplantation is an accepted therapeutic modality for end-stage pulmonary diseases [4]. The results of lung transplantation greatly depend on the ability to maintain adequate immunosuppression to prevent allograft rejection. Obliterative bronchiolitis (OB), regarded as a form of chronic rejection, is the leading cause of long-term functional impairment and mortality after lung transplantation. Refractory acute rejection (RAR) is among the factors leading to the development of OB [1]. Since the standard cyclosporine-based immunosuppressive treatment has been found in a certain percentage of patients to be inadequate in both settings, alternative immunosuppressive strategies are required. Tacrolimus (Tac) is a macrolide immunosuppressant with properties similar to cyclosporin A (CyA), but significantly more powerful [12]. The role of Tac as a rescue treatment in patients with refractory rejection has been established after heart, kidney and liver transplantation, but still has to be completely assessed after lung transplantation [5, 8, 10]. The aim of this study was therefore to analyse the results of switching from CyA to Tac in the treatment of RAR and OB after lung transplantation in a single institution.

Patients and methods

From November 1989 to May 1999, 291 patients underwent lung transplantation at the Department of Cardio-thoracic Surgery of the University of Vienna, Austria. In 19 patients the immunosuppressive treatment was changed from CyA (Sandimmun Neoral, Novartis) to Tac (Prograf, Fujisawa). These patients form the cohort of this study.

Immunosuppression

The maintenance immunosuppressive therapy after lung transplantation was based on a triple-drug combination of CyA,

prednisone and mycophenolate mofetil (Cellcept; Roche). Only five patients, receiving transplants early and being on azathioprine (Imurek; Glaxo Wellcome)-based immunosuppression, had been switched to mycophenolate mofetil prior to the subsequent switch from CyA to Tac. All patients received an induction therapy with antithymocyte globulin (ATG; Merieux) at a dose of 2.5 mg/kg. Prednisone was tapered from 1 mg/kg per day to 0.15 mg/kg per day 6 months after transplantation. CyA blood trough levels were maintained at 350 ng/ml in the 1st year after transplantation and then reduced to 200–250 ng/ml. The dose of azathioprine (2 mg/kg per day) or mycophenolate mofetil (3 g/day) was reduced in cases of leucopenia or thrombocytopenia.

Routine bronchoscopy with transbronchial biopsy and bronchoalveolar lavage was performed in all patients 10–14 days after the operation, then after 1 month, 3 months, 6 months and 12 months, and then yearly or in cases of clinical signs of rejection. The diagnosis of acute rejection was established on the basis of the results of the transbronchial biopsy or if a decline of the forced expiratory volume (FEV_1) higher than 10% was observed, provided any infectious disease had been excluded. The definition of RAR encompassed both recurrent acute rejection and ongoing refractory rejection. Recurrent acute rejection was defined as the presence of two or more episodes of acute rejection within 3 months. A diagnosis of ongoing refractory rejection was established in cases of acute rejection which did not respond to the standard treatment with steroids, ATG or OKT3.

The diagnosis of OB was based on the criteria for chronic dysfunction of the International Society for Heart and Lung Transplantation [3], when no other explanation for the sustained reduction of the pulmonary function was found.

The result of conversion to Tac in the group of patients with RAR was considered successful if no episodes of acute rejection were observed within 3 months after switching. In the group of patients with OB the switch to Tac was considered successful on the basis of the number of acute rejections observed within the first 3 months from switching, and according to the reduction of the decline of FEV_1 in the following 6 months. Monitoring of rejection was performed every 2 weeks within 3 months before the switch and in the 3 months after it.

Statistical analysis

Results were expressed as the mean ± standard deviation. Pre- and post-switch data were compared with Student's *t*-test and the Wilcoxon signed-rank test. Statistical significance was defined as a *P*-level of less than 0.05.

Results

Nineteen patients entered the study; mean age was 41.3 ± 13.1 years. Nine patients were male and ten female. The indication for lung transplantation was primary pulmonary hypertension in 8 patients, chronic obstructive pulmonary disease (COPD) in 5 patients, pulmonary fibrosis in 4 patients, cystic fibrosis in 1 patient and bronchiectasis in 1 patient. A single lung transplantation was performed in 7 patients and a bilateral transplantation in 12.

The indication for switching from CyA to Tac was OB in 11 patients and RAR in 8 patients. Mean time from transplantation to the switch was 25.6 ± 22.8 months (26.7 ± 17.7 months in patients with OB and 23 ± 28.3 months in patients with RAR); and mean follow-up after switching was 14.2 ± 10.2 months (12.7 ± 9.7 months in patients with OB and 16.2 ± 11.1 months in patients with RAR). Sixteen of nineteen patients are still alive, and 3 have died due to sepsis, pancreas carcinoma and bronchiolitis obliterans organizing pneumonia (BOOP) 10 months, 5 months, and 1.5 months after switching, respectively. The mean CyA blood level within 3 months before the switch was 223.6 ± 92.1 ng/ml. The mean Tac level within 3 months after switching was 11.7 ± 2.9 ng/ml.

Refractory acute rejection

In the group of eight patients whose treatment was converted to Tac owing to RAR (recurrent acute rejection in three patients and ongoing resistant rejection in five patients), the mean number of acute rejection episodes before conversion to Tac was 1.5 ± 0.7 episodes/patient per 100 days (histologically proven in 95.4%). After switching no other episodes of rejection were observed within 3 months ($P = 0.02$). In four patients with a 1-year follow-up, no episodes of rejection were

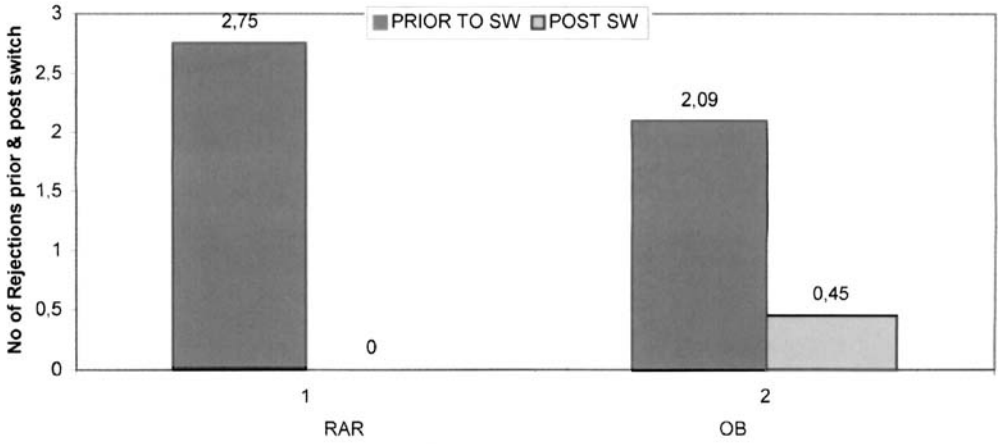

Fig. 1 Total number of acute rejections before and after switching (*SW*) in refractory acute rejection (*RAR*; $n = 8$) and obliterative bronchiolitis (*OB*; $n = 11$) groups

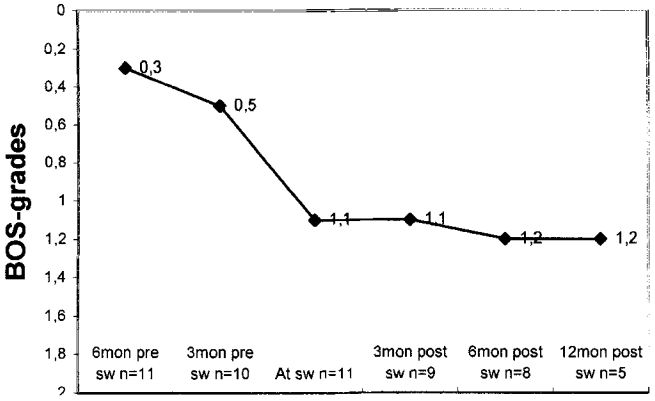

Fig. 2 Bronchiolitis obliterans syndrome (*BOS*) grades time course

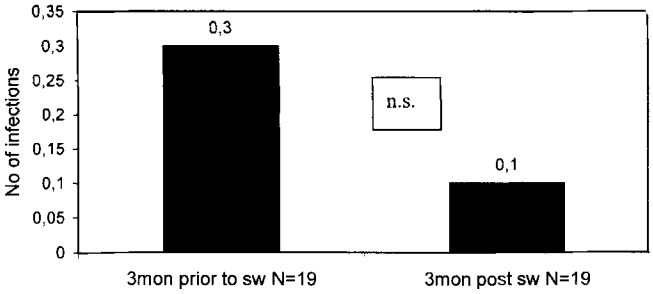

Fig. 4 Total number of infections before and after switching

detected (Fig. 1). In seven patients with a follow-up of at least 3 months after switching, the FEV_1 was 2.6 ± 1.0 l (67 ± 22.9%) 3 months before the switch, reduced to 2.4 ± 0.6 l (62.4 ± 14%) at the time of switching and to 2.3 ± 0.9 l (56.7 ± 17.3%) 3 months after the switch. The mean number of infections requiring i.v. treatment was 0.4 ± 0.5 to 0.3 ± 0.5 episodes (P = n.s.) during the 3 months before and after switching in this group.

Obliterative bronchiolitis

In 11 patients the immunosuppressive treatment was converted to Tac because of OB. The mean OB grade at the time of switching was 1.1, which stabilized over a period of 1 year after the switch (Fig. 2). The best mean FEV_1 value after transplantation was 2.7 ± 0.9 l (79.1 ± 17.9% of predicted). Six months before switching, the mean FEV_1 value was 2.3 ± 0.7 l (64.8 ± 13.2% of predicted), which decreased to 1.9 ± 0.7 l (56.8 ± 17.7%) at the time of the switch and to 1.4 ± 0.7 l (44.8 ± 18.7%) 6 months after conversion in eight patients with a follow-up of at least 6 months after switching (Fig. 3). No significant reduction of the decline of FEV_1 could be observed within 6 months after the switch in this group. The total number of acute rejections until conversion to Tac was 2.1 ± 2.1. The mean number of acute rejection episodes was 0.4 ± 0.5 and 0.1 ± 0.3 within the last 3 months before and the first 3 months after switching. No statistical change of the number of acute rejections could be observed (P = 0.08).

The mean number of infections requiring i.v. treatment in OB group was 0.3 ± 0.6 and zero (P = 0.18) during the 3 months before and after switching, respectively (Fig. 4). In both groups the mean serum creatinine measured 3 months before and after conversion to Tac rose from 1.4 ± 0.4 mg/100 ml to 1.8 ± 2.5 mg/100 ml.

Discussion

Since its introduction in clinical practice, cyclosporine-based immunosuppression has allowed a significant improvement in the results of lung transplantation [11].

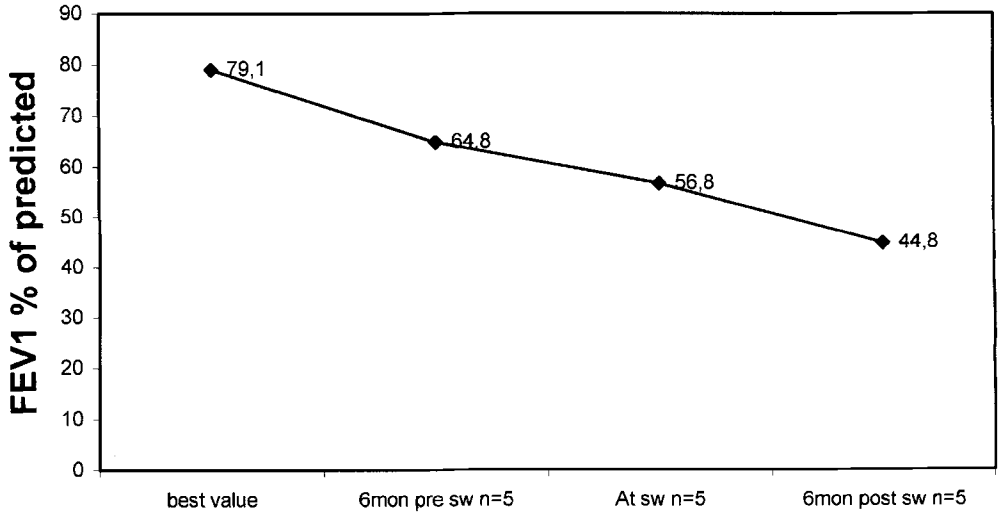

Fig. 3 Forced expiratory volume (FEV_1) as a percentage of predicted time course in OB group

However, this approach may be inadequate in the treatment of RAR and OB.

The importance of adequately treating RAR is related to the necessity not only of controlling the acute deterioration of the pulmonary function that is associated with this event, but also to prevent the development of chronic rejection. The incidence and the frequency of RAR after lung transplantation is in fact related to the development of OB, which is the leading cause of late functional deterioration and mortality after lung transplantation [1].

Different therapeutic strategies have been proposed in order to improve the results of the treatment of RAR and OB. Among these, the use of total lymphoid irradiation, methotrexate and aerosolized cyclosporine have been associated with promising results, but still have to be validated [2, 7, 14]. The role of the conversion from the standard CyA-based immunosuppression to a Tac-based treatment in these settings is unclear.

The effectiveness of Tac as a salvage immunosuppressive treatment has been already demonstrated in other solid-organ transplantations such as after cardiac, renal and liver transplants [5, 8, 10]. However, there are only a few documented reports on small cohorts of patients about the use of Tac as a salvage treatment after lung transplantation. The usual indications for converting the standard CyA-based immunosuppressive treatment to a Tac-based strategy are the presence of recurrent and steroid-resistant acute rejection, OB and the presence of side effects of CyA such as gingival hyperplasia, hirsutism and hypertension.

Onsager et al. have evaluated the efficacy of Tac in the treatment of RAR following lung transplantation and have observed a remission of the acute rejection episodes in 73% of the treated patients and a stabilization of the pulmonary functions in 60% of them. The time of the switch to Tac appears to have great importance for the success of the treatment, since early-treated patients tend to have a better outcome [13].

In another study, Horning et al. have also evaluated the role of the switch to Tac in the treatment of RAR in a group of patients after lung transplantation, and have observed a reduction both in the number and in the grade of acute rejection episodes after conversion [6].

A further point which has been preliminarily evaluated is the efficacy of the conversion from CyA to Tac in patients with OB. Kesten et al. have observed a significant reduction of the decline of FEV_1 in patients with OB after the administration of Tac [9]. However, this limited number of trials is based on small groups of patients and does not allow us to draw definitive conclusions. Because of these limitations, we decided to evaluate our experience about the effectiveness of switching to Tac.

In the present study the role of the switch from CyA to Tac in the treatment of RAR and OB after lung transplantation was retrospectively assessed. The success of the use of Tac in patients with RAR was established on the basis of the absence of further episodes of acute rejection within 3 months from switching to Tac. In the group of patients which had been converted to Tac due to the presence of OB, the treatment was considered successful if a significant reduction of acute rejection episodes was observed within the first 3 months from switching, and on the basis of the decrease in decline of FEV_1 after starting the treatment with Tac.

The results in the treatment of RAR were in our experience extremely encouraging, since no episodes of acute rejections were observed in any of the treated patients within 100 days after switching, and in all patients with 1-year follow-up after switching, compared with an incidence of 0.9 episodes/patient per 100 days before conversion to Tac ($P=0.02$). The potential influence of these data on the onset of OB has to be evaluated after a longer follow-up and in a larger cohort of patients.

In patients with OB, we could not observe a significant reduction of the decline of FEV_1 after the switch in our study. Further investigations with more patients are required to clarify the effects of the switch from CyA to Tac on the course of OB.

The possible drawbacks of the conversion to Tac have to be considered. In this study the number of infectious episodes tended to be lower after the conversion to Tac. Although the mean serum creatinine level was higher after switching, no major morbidity was observed.

In conclusion, in our experience the switch from CyA to Tac proved to be extremely useful in the treatment of RAR and should be considered as an indication for switching from CyA to Tac. In patients with RAR, no further acute rejection episodes were observed within 100 days from the start of the treatment. Even in those patients with a 1-year follow-up after switching, no rejection could be observed. In the treatment of OB, our data could not confirm a reduction of the decline of the pulmonary function. Of great importance is the fact that the beneficial results on the decline of FEV_1 were not obtained at the price of a higher number of infections. Further studies in a larger cohort of patients are required to confirm the impact of these findings on the longer follow-up.

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