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Tacrolimus for Treatment of Bronchiolitis Obliterans Syndrome After Unilateral and Bilateral Lung Transplantation

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BRONCHIOLITIS OBLITERANS SYNDROME (BOS) represents the major factor influencing long-term clinical outcome after lung transplantation.[1] The registery data of the International Society for Heart and Lung Transplantation show a significant morbidity from BOS raising from 10.9% at 1 year posttransplant to 29.5% at 5 years follow-up. BOS represents the leading cause of death in the late postoperative course after lung transplantation. BOS has been correlated with a variety of parameters, but chronic graft rejection is considered as major cause of BOS.[2] Therefore augmented immunosuppressive regimens are under investigation.[3]

The effect of switch from cyclosporine A to tacrolimus in patients with new onset of BOS is reported in this study.

MATERIALS AND METHODS

The study group was comprised of 26 consecutive patients undergoing unilateral or bilateral lung transplantation. Mean age at time of transplant was 46 years (±16 years); 12 patients were female, 14 male. Twelve patients received a bilateral sequential lung transplantation for cystic fibrosis or alpha 1 AT deficiency as underlying disease. Fourteen patients received a unilateral lung transplant for pulmonary fibrosis or end-stage COPD. Initial immunosuppression consisted of IV MMF (3 g/24 hours) and continuous intravenous cyclosporine (1.5 mg/kg 24 hours) was switched to oral administration on POD 3 to 7. Intraoperatively, 500 mg methylprednisolone was administered. Prednisolone dosage was tapered from 100 mg on POD 1 to 10 mg of POD 8. Triple-drug immunosuppression was maintained in all patients with CyA blood target levels of 250 ng/mL.

All patients were monitored for the onset of BOS by scheduled spirometry. According to the definition of BOS stage I, a significant (>20%) and reproducible loss in FEV1 below the best posttransplant values was the indication for the switch of the calcineurin inhibitor from cyclosporine A to tacrolimus. Tacrolimus was given orally and adjusted for a blood level of 10 ng/mL. The other components of the immunosuppressive regimen (ie, mycophenolate mofetil and steroid dosage) were left unchanged. CMV pneumonitis as cause of the obstructive airway changes was ruled out by monitoring for seroconversion and CMV-PCR in all patients prior to augmentation of immunosuppression.

RESULTS

During a median follow-up period of 392 days, seven patients (27%) developed the criteria for BOS stage I, which represented the indication for switch to tacrolimus at a median of 165 days posttransplant.

Mean FEV1 at time of switch was 1570 mL increasing to 1740 mL (change: +11%) 1 month postswitch, to 2270 mL (+45%, $P < .05$) at 6 months and 2050 mL (+31%, $P < .05$) at 12 months. In the tacrolimus-treated group, there were no fatalities from acute rejection or from chronic rejection (bronchiolitis obliterans). In this group, all patients except one are well and alive at follow-up. One of the seven patients switched to tacrolimus did not improve and subsequently died of respiratory insufficiency. At autopsy, human herpes virus 6 (HHV6) pneumonitis was proven as the cause of obliterative airway changes.

CONCLUSIONS

In this intervention study, change of the calcineurin antagonist from cyclosporine to tacrolimus proved to be effective in the treatment of new-onset BOS. The progressive airway obstruction reverted with a significant and sustained improvement in FEV1 at 6 and 12 months follow-up. Although the power of this study is limited, the investigated cohort compares favorably to historic controls. Discrimination of the cause of airway obstruction should be attempted and viral pneumonitis should be ruled out serologically. Further confirmation of these preliminary data is needed by a prospective randomized trial.

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