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ORIGINAL ARTICLE

Antithymocyte globulin induction therapy improves survival in lung transplantation for cystic fibrosis

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Summary

Cystic fibrosis (CF) is an inherited condition that leads to respiratory failure and is the third most common indication for adult bilateral lung transplantation (LuTX). In contrast to other lung diseases, the immune system of CF patients is up-regulated and we therefore hypothesized that these patients would benefit from induction therapy. In the current study, we investigated the impact of antithymocyte globulin (ATG) induction therapy in CF patients after LuTX. One hundred and forty six patients who underwent LuTX for CF at our centre between January 1999 and December 2010 were included in the study and retrospectively analysed. They were divided into two groups according to the immunosuppressive protocol: group-A ($n = 103$) with and group-B ($n = 43$) without induction therapy on top of the basic calcineurin inhibitor based triple immunosuppression with mycophenolate mofetil and steroids. Perioperative survival was significantly better in the ATG group, a benefit sustained for the entire follow-up. ATG induction resulted in a significantly lower incidence of acute rejections without an increase in infectious complications. Taken together, our results indicate that ATG induction therapy confers a significant survival benefit in CF patients undergoing LuTX and reduces rejection. We advocate the use of induction therapy in this patient cohort.

Introduction

Lung transplantation has been established as an appropriate ultimate treatment option in end-stage lung disease [1]. Cystic fibrosis (CF) is among the most common indications for lung transplantation with 17% of the adults undergoing lung transplantation between 1995 and 2010 according to the 2011 Registry of the International Society of Heart and Lung Transplantation (ISHLT) [2,3]. However, in comparison to other solid-organ transplants, the outcome of clinical lung transplantation remains worse, even though the gap has narrowed dramatically. Over the past years, survival rates improved owing to better organ preservation, surgical techniques and intensive-care management. The major problem in the early period after LUTX remains acute rejection and infection, both of which are pronounced in CF patients. The long-term success of clinical lung transplantation is mainly limited by late allograft failure [3].

The use of induction therapy after lung transplantation is discussed controversially in the scientific literature [4,5]. About 50% of lung transplant recipients included in the ISHLT registry have received induction therapy. Agents primarily used are polyclonal antilymphocyte preparations, interleukin-2 receptor antagonists and anti-CD52 antibodies (Alemtuzumab). Induction therapy has been used in solid-organ transplantation to minimize the risk of early acute rejection and to delay the introduction of a calcineurin inhibitor, especially in patients with renal impairment. Although no large scale, randomized, prospective trial has been performed, at least three studies have shown that induction therapy decreased the incidence of early acute rejection after lung transplantation [6–8]. Nonetheless, critics of induction have stressed that

there is no significant difference in long-term outcome with regard to BO and survival, and that an increased frequency of infectious complications and post-transplant lymphoproliferative disease (PTLD) can be observed in patients who receive induction agents [9,10]. In addition, the most effective induction agent remains uncertain.

Cystic fibrosis patients constitute a specific group among lung transplant recipients: in general, they are younger at time of transplantation, chronically infected, as their early childhood and immunologically highly up-regulated. In contrast, patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis are older, usually not infected and consistently immunosuppressed in some way at the time of transplantation. Therefore, one could assume that CF patients would benefit the most from induction therapy.

In the current study, we hypothesized that induction therapy with rabbit-antithymocyte-globulin (ATG) used in patients after LuTX for CF would lead to an improvement in survival and a decrease in acute allograft rejection.

Patients and methods

All patients who underwent lung transplantation for CF at the Department of Thoracic Surgery at the General Hospital Vienna, Medical University Vienna, between January 1999 and December 2010 were included in the current study in a consecutive manner. In addition, subgroup analyses were performed for two periods: 1999–2004 and 2005–2010.

Surgical technique

Surgical approach was either a uni- or bilateral anterolateral thoracotomy in the 4th or 5th intercostal space or a bilateral thoracotomy with a transverse sternotomy (Clamshell incision). After a standard pneumonectomy and preparation of the hilum, the first step of the implantation was the bronchial anastomosis, which was performed in an end-to-end technique using a single running suture technique with 4/0 or 5/0 polydioxanone suture. Thereafter, the atrial anastomosis was sutured using 4/0 prolene and the arterial anastomosis with 5/0 prolene. After retro- and antegrade flushing, controlled reperfusion was performed. Double lung transplantation was performed in the sequential technique. Suctioned blood was processed through a cell saver while the recipient bronchus was closed and was discarded as long as the recipient bronchus was open.

Immunosuppressive protocol

All patients received a triple immunosuppressive therapy, including steroids and MMF in combination with either Tacrolimus in 128 patients (88%) or Cyclosporine A in 18 patients (12%). The choice of calcineurin inhibitor was time dependent: all patients transplanted prior to 2000 received cyclosporine, whereas tacrolimus was used as medication thereafter. Target trough levels of cyclosporine were 250–300 ng/ml during the first postoperative year, 150–250 ng/ml during the second year and 100–150 ng/ml thereafter. Target trough levels for tacrolimus were 10–15 ng/ml during the first postoperative year and 8–10 ng/ml thereafter. Mycophenolate mofetil dose was 3 g/day within the first postoperative year and 2 g/day thereafter; dose reduction was performed if patients developed side-effects. Prednisolone was administered according centre protocol.

Induction therapy was first started in 1997 in the context of various immunosuppression trials. Starting in 2005, when a subgroup analysis revealed an increased survival in patients who received induction therapy after lung transplantation for cystic fibrosis, all patients with CF have received ATG induction therapy. Antithymocyte globulin (ATG-Fresenius® S; Biotech, Munich, Germany) was administered at a dose of 2 mg/kg bodyweight immediately after arrival on the ICU and discontinued on POD 5.

Anti-infectious prophylaxis and therapy

All patients routinely received double antibiotic prophylaxis according to pretransplant resistance testing. Antifungal medication was started in cases of positive fungal cultures whenever indicated.

An antibiotic inhalation therapy was performed for a minimum of 4 weeks with Colistin or Tobramycin, according to bacteriology. Furthermore, all patients received a 3 months inhalation therapy with Amphotericin B.

All at-risk lung transplant recipients received a combined prophylaxis with IV Ganciclovir for 2 weeks and four doses (Days 1, 7, 14 and 21 post-transplant) of CMV IVIg (Cytotect; Biotest GmbH, Vienna, Austria), followed by Valganciclovir for 3 months. After December 2004, all high-risk patients (D+/R−) were treated with Valganciclovir for 12 months, again starting with IV Ganciclovir for 2 weeks and four doses of CMV IVIg. All patients received Valganciclovir 900 mg/day. Dose adjustment was made according to renal function; Valganciclovir was decreased to 450 mg/day for a creatinine clearance of <50 ml/min.

All patients received livelong trimethoprim as pneumocystis jirovecii prophylaxis.

Follow up and management of acute rejection episodes

Surveillance bronchoscopies with transbronchial biopsy were performed at 2 weeks, 1, 2, 3, 6 and 12 months after transplantation. In addition, bronchoscopies with biopsy

were performed as clinically indicated for suspected rejection, infection, or other pulmonary problems. All diagnoses of acute rejection were confirmed with biopsy specimens, and standard histological criteria and grading schemes [11] were used. The first episode of acute rejection was treated with a 3-day course of high-dose methylprednisolone (500–1000 mg/day), and, if the maintenance prednisone dose had been tapered, it gradually decreased back to the previous dose over 2–4 weeks.

Tacrolimus was substituted for Cyclosporine in the regimen of recipients with persistent or recurrent acute rejection. Furthermore, patients received antilymphocytic therapy with ATG or OKT3.

Pulmonary function tests were performed at regular intervals, and BOS was diagnosed by the guidelines of the International Society for Heart and Lung Transplantation.

Cumulative rejection scores

We defined the cumulative acute rejection A-score as the sum of all A-scores for each subject. Likewise, we defined the cumulative lymphocytic bronchitis B-score as the sum of all B-scores for each subject, excluding B-scores in the setting of a confirmed bacterial or viral respiratory tract infection.

Microbiology

Pretransplant microbiology from sputum or lavage and intraoperative bronchiolo-alveolar-lavage of the recipient were recorded from the patient charts.

Statistics

The data of these patients were retrospectively analysed using SPSS 16.0 for Windows (SPSS, Chicago, IL, USA).

Continuous variables were expressed as mean ± standard deviation and analysed using the *t*-test. Standard Kaplan–Meier survival technique was used to analyse survival, freedom from CMV infection/disease, freedom from acute rejection and freedom from BOS. Dichotomous variables were compared using Pearson's Chi-squared test. Fisher's exact test was used in case of expected cells are less than five. Continuous variables were compared using students test in case of normal distribution. A *P*-value less than 0.05 was considered to be significant. Mann–Whitney *U*-test was used in cases of non normal distributed variables. Most important factors for 90-day mortality were entered into a binary regression model.

Results

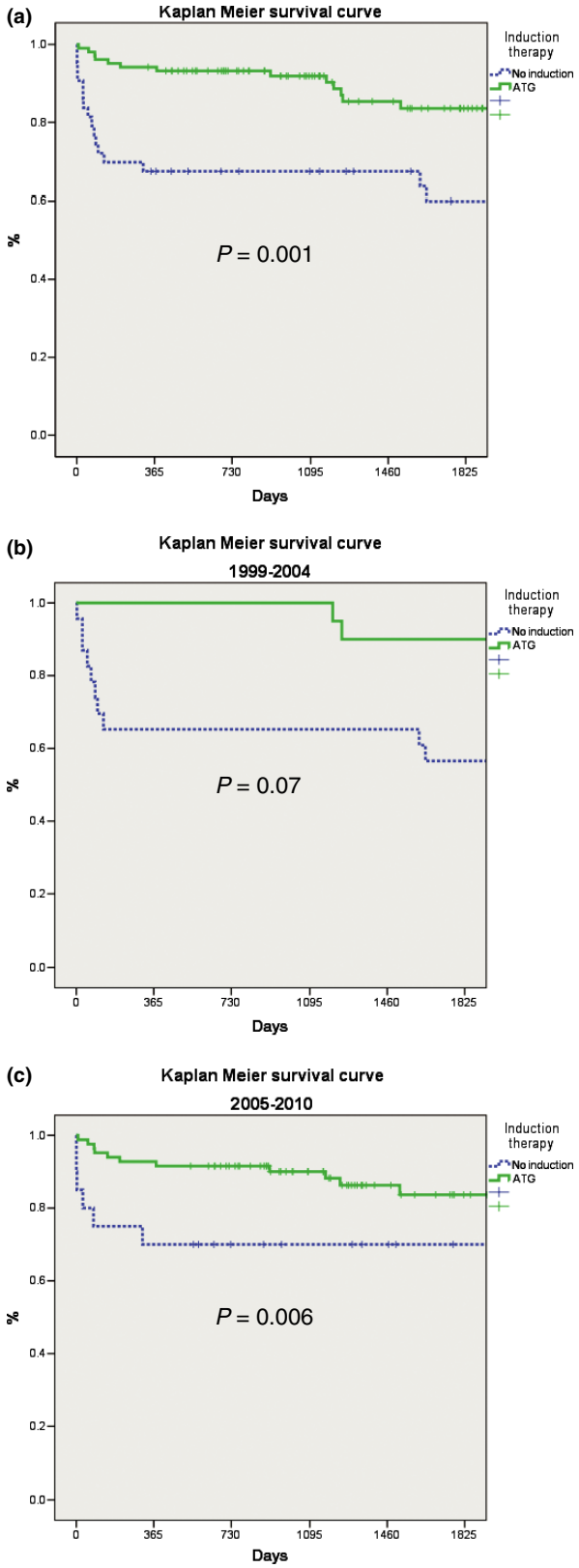
In a 12-year period between 1999 and 2010, 146 CF patients underwent lung transplantation at a single centre (Medical University Vienna). Demographic data are shown in Table 1.

Sixty-seven (46%) patients were men, 79 (54%) women. One hundred and forty one (97%) patients underwent double lung transplantation, one (1%) a heart-lung transplantation and four (2%) a single lung transplantation. Mean age at time of transplant was 25.4 ± 8.7 years (5.7–52.6).

Table 1. Cumulative A- and B-scores after 3 months and 1 year.

	ATG	No induction	
Group	Group A	Group B	*P*-value
	103	43	
Age (years)	24.9 ± 8.0	26.7 ± 10.2	0.32
Sex (m/f)	48/55 (47%/53%)	19/24 (44%/56%)	0.56
DLuTX/SluTX	100/3 (97%/3%)	42/1 (98%/2%)	
ECMO preTX (*n*)	3 (3%)	10 (23%)	0.001
Intubated at TX (*n*)	10 (10%)	14 (33%)	0.001
High urgent status (*n*)	14 (14%)	15 (35%)	0.004
Dead/alive	16/87 (16%/84%)	18/25 (42%/58%)	0.001
Follow-up (days)	1530 ± 965	1497 ± 1462	0.87
In-hospital mortality	4 (4%)	10 (23%)	0.004
Day of extubation (days)	4.6 ± 8.1	9.6 ± 15.3	0.6
ICU stay (days)	15.0 ± 23.7	17.3 ± 23.5	0.6
Hospital stay (days)	34.8 ± 32.8	37.2 ± 32.3	0.02
CMV status			
Donor+/Recipent−	24 (23%)	11 (26%)	
Donor+/Recipient+	46 (45%)	14 (33%)	
Donor−/Recipient+	14 (14%)	9 (21%)	
Donor−/Recipient−	13 (13%)	4 (9%)	
Missing data	1 (1%)	0	
Primary immunosupression			
Cyclosporine A	2 (2%)	16 (37%)	0.05
FK-506	101 (98%)	27 (63%)	
PreTX bacteriology			
Burkholderia cepacia	7 (7%)	4 (9%)	0.13
MRSA	9 (9%)	0	
Multiresistent PA	8 (8%)	6 (14%)	
PA	73 (71%)	36 (84%)	
Staphylococcus aureus	19 (19%)	10 (23%)	
Stenotrophomonas	3 (3%)	0	
Acinetobacter	3 (3%)	0	
Achromobacter xyloxidans	3 (3%)	0	
PreTX mycology			
Aspergillus fumigatus	9 (9%)	3 (7%)	0.1
Candida albicans	12 (12%)	12 (28%)	

ATG, antithymocyte globuline; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MRSA, methicillin resistant *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*; PreTX, pretransplantation; Retx, retransplantation; DLuTX/SLuTX, double lung transplantation/single lung transplantation.



Twenty-four patients (16%) were ventilator dependent, 13 of them on ECMO support at time of transplantation.

In 103 patients, (70%) (group A) induction therapy with ATG was administered, and in 43 (30%) cases, no induction agent was (group B) used. The mean time of follow up was 1520 ± 1129 days (range 1–4677).

In the first study period between 1999 and 2004, 23 patients received no induction therapy and 20 patients received ATG induction therapy. A survival analysis in 2004 revealed a significant decrease in mortality in patients with induction therapy. Hence, we leaned more towards induction therapy beginning in 2005 with a total of 83 patients with induction and only 20 patients without induction therapy in the second time period analysed.

Survival

Patients who received ATG as induction in the first time period had 1-, 3- and 5-year survival of 95%, 93% and 84% respectively. In contrast, the survival of patients without induction therapy was 67%, 67% and 60% respectively (log rank group A vs. group B $P < 0.05$), (Fig. 1a). A similar difference was observed in the second time period analysed. (Fig. 1b) An analysis of all patients who received ATG as induction revealed a 1-, 3- and 5-year survival of 94%, 92% and 84% respectively. In contrast, the survival of patients without induction therapy was 67%, 67% and 60% respectively (log rank group A vs. group B; $P < 0.05$; Fig. 1c).

The survival advantage of induction therapy persisted independent of the preoperative status, as exclusion of patients on ECMO at the time of transplantation revealed also a significant survival difference.

Binary logistic regression identified ATG induction therapy [odds ratio 0.176 (0.047–0.662), $P = 0.01$] and primary immunosuppression with Tacrolimus [odds ratio 0.155 (0.031–0.779), $P = 0.024$] as independent negative predictors for 90-day mortality (Table 2).

High urgent listing and pretransplant status

Fourteen patients of group A and 15 patients of group B were listed on a high urgent status, a difference that did not

Figure 1 ATG induction therapy results in significantly improved survival in CF patients after lung transplantation. (a) Survival rates of patients with ATG versus patients without ATG in period I. (b) Survival rates of patients with ATG versus patients without ATG in period II. (c) Survival rates of patients with ATG versus patients without ATG in the complete study period.

Table 2. Multivariate analysis risk factors – survival after LuTX.

				95% Confidence interval	
	Wald	*P*-value	Odds ratio	Lower value	Upper value
ATG induction	6.612	0.010	0.176	0.047	0.662
Period (1999–2004 versus 2005–2010)	0.128	0.721	1.365	0.248	7.499
Tacrolimus as primary immunosupression	5.120	0.024	0.155	0.031	0.779
Preoperative ECMO	0.495	0.482	2.097	0.266	16.498
High urgent listing	0.046	0.830	1.213	0.208	7.085

ATG, antithymocyte globuline; ECMO, extracorporeal membrane oxygenation.

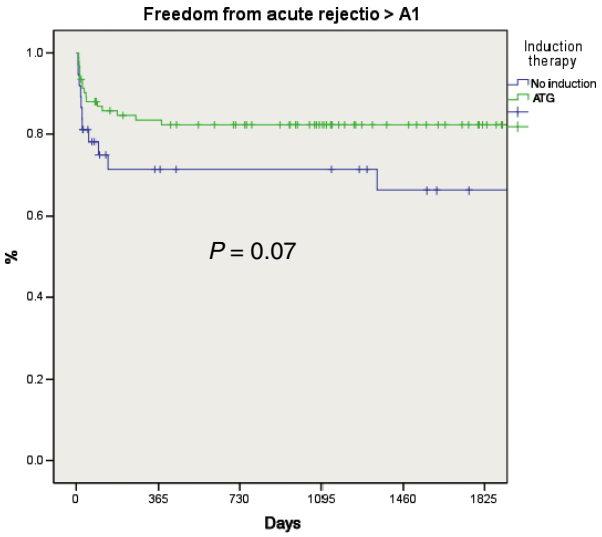


Figure 2 Trend but no statistical significance in reduction of acute rejection episodes through induction therapy.

reach statistical significance. In group A, 10 patients were intubated prior to transplantation, three of them were also on ECMO support, in group B, 15 patients were intubated at time of transplant and a higher number (n = 10) was on ECMO support (P = 0.001).

Infection

In group A, six patients died because of infectious complications in the first postoperative year, whereas in group B, nine patients died in the same period.

Rejection

The use of induction therapy with ATG compared with no induction therapy resulted in fewer episodes of acute rejection ≥ grade A1 with a freedom from rejection of 86% in group A versus 74% group B within the first 100 days post-transplant (P = 0.07) (Fig. 2). Cumulative A- scores [12] after 100 days (group A 0.75 ± 1.0 vs. group B 1.2 ± 0.2, P = 0.043) and after 1 year (group A 1.3 ± 0.21 vs. group B 1.7 ± 0.25, P = 0.039) were significantly different between the groups (Table 3). The impact of induction therapy was independent of the preoperative status.

Freedom from high grad lymphocytic bronchiolitis was not different between both groups (P = ns) (Fig. 3).

Table 3. Complications post LuTX : ATG induction vs no induction.

	ATG	No induction	
	A	B	
n	103	43	
BOS	16 (16%)	6 (14%)	0.01
Time to BOS (days)	1535 ± 572	1062 ± 347	0.14
Reason for death			
Non CMV infection	6 (6%)	8 (19%)	
CMV infection	0	1 (2%)	
Graft failure	0	2 (5%)	
BOS	3 (3%)	1 (2%)	
ReTX	6 (6%)	4 (9%)	0.33
Indication for ReTX			
BOS	6 (6%)	1 (2%)	0.05
POF	1 (2%)	3 (7%)	
Time to ReTX (d)	1465 ± 831	369 ± 688	
PTLD	3 (3%)	1 (2%)	0.6
Time to PTLD (d)	866 ± 931	477	0.7
Aspergillus	10 (10%)	1 (2%)	0.17
CMV			
Viremia	22 (22%)	5 (12%)	0.28
Disease	9 (9%)	1 (2%)	0.24

ATG, antithymocyte globuline; BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus; PTLD, post-transplant lymphoproliferative disorder; POF, primary organ failure.

Retransplantation

Retransplantation was performed in six patients of group A and in four patients of group B, indications for ReTX was BOS in six patients of group A, in group B, three patients had a need for ReTX because of primary graft failure and just one because of BOS.

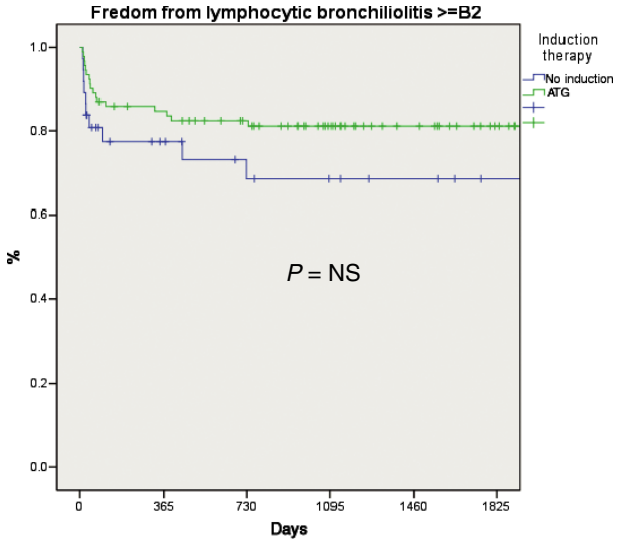


Figure 3 No significant difference in freedom form bronchiolitis obliterans between induction and no induction therapy.

Microbiology pre- and peritransplantation

The microbiology of both patient groups is depicted in Table 4. In both cohorts resistant strains of Pseudomonas, *Burkholderia cepacia*, Stenotrophomonas and Methicillin-resistant *Staphylococcus aureus* were cultured at time of transplantation. Interestingly, the type of cultured bacteria had no significant influence on postoperative survival. In particular, seven patients of the induction group were infected with the most dreaded bacteria in CF patients *Burkholderia cepacia* (on contrast with only four in group B) and all of them survived.

Colonization with *Aspergillus fumigatus* was frequent in both groups (nine in group A and three in group B), but none of these patients developed an invasive Aspergillus infection postoperatively. All the Aspergillus colonized patients received antifungal prophylaxis with Voriconazole for a minimum of 3 months.

CMV infections and CMV disease

Twenty-four patients of group A and 11 of group B were at high risk for CMV infections (D+/R− at time of LuTX).

Table 4. Cumulative A and B scores after 3 months and 1 year.

	ATG	No induction	*P*
n	103	43	
Cum A100 score	0.75 ± 1.0	1.2 ± 0.2	0.043
Cum A1a score	1.3 ± 0.21	1.7 ± 0.25	0.039
Cum B100 score	1.76 ± 0.17	2.0 ± 0.23	0.13
Cum B1a score	3.1 ± 0.21	2.9 ± 0.29	0.6

ATG, antithymocyte globulin.

Nine patients of the induction group developed CMV disease with a mean onset after 222 ± 38 days postTX, compared with only one patient in the noninduction group. All patients received a therapy with IV Ganciclovir for a minimum of 2 weeks in combination with CMV hyperimmunoglobuline followed by oral Valganciclovir until CMV–PCR was lower than 600 copies/ml. One patient in the noninduction group died because of CMV related problems.

CMV viremia and syndrome was frequent in both groups with a trend in earlier onset in the induction group without reaching statistical significance.

Pulmonary function and BOS

There was no difference between both groups regarding pulmonary function. The incidence of BOS did not differ between both study groups: 16 patients of the induction group and six of the noninduced patients developed BOS with a mean onset after 1525 ± 572 days and 1062 ± 347 days respectively (P = ns). Because of chronic organ dysfunction, seven patients underwent retransplantation, six in group A and one in group B (P = ns).

PTLD

Three patients of group A and one patient of group B developed PTLD, time-to-malignancy was 866 ± 931 days in the induction group and 477 in group B. Because of the small number of patients, the difference reached no statistical significance. Patients were treated using chemotherapy (CHOP protocol) and Rituximab accompanied by dose reduction of the maintenance immunosuppression. All patients are alive and had no recurrence of PTLD until now.

Discussion

Taken together, the data of the current study demonstrate a significant survival benefit in CF patients who received induction therapy with polyclonal lymphocytic antibodies (ATG) on top of the basic triple immunosuppression after LUTX. Of note, this survival benefit can be observed independent of the transplant era as demonstrated by the analysis of patients transplanted between 1999 and 2004. In this time period, the number of patients with induction was similar to the patients without induction; still the survival was markedly improved by induction therapy.

In addition, ATG induction had a beneficial impact on rejection: the cumulative A-scores both at 100 days and at 1-year were significantly lower in the ATG group compared with patients who did not receive induction therapy.

We hypothesize that the survival benefit in the ATG group is based on the following factors: All CF patients are chronically infected and colonized, in many instances

with multiresistant bacteria, at the time-point of transplantation leading to an up-regulated immune system. The chronic infection of these patients gives a permanent stimulus to the immune system leading to leucocytosis and increased levels of cytokines in these patients at time of transplantation. Induction therapy suppresses the immune system perioperatively to a much higher degree as compared with basic immunosuppression alone [13,14]. However, the risk of infection in this highly sensitive perioperative period is counterbalanced by patient-tailored antibiotic therapy, which is administered according to the pretransplant microbiology resistance testing. All patients are closely monitored and treatment is initiated immediately as soon as any signs of infection are detected in the controlled and specialized environment of the transplant intensive care unit (ICU). This hypothesis is supported by our results, where we could clearly demonstrate that ATG did not lead to an increased rate of severe infectious complications. On the opposite, the mortality from infection was even lower in this group with higher immunosuppression.

The effect of the aggressive immunosuppression using ATG induction therapy is sustained with an overall lower rejection rate and mortality within the first 3 months. Therefore, the vicious circle was interrupted: we usually observed rejections beyond 1-month postoperatively, which were treated with bolus immunosuppression. This in turn increased dramatically the risk of infection with poly-resistant strains at a time-point where the patients are no longer in the ICU and under first-line antibiotic therapy with a switch in bacterial resistance. In many instances, the patients died from infection under this specific constellation.

With this model in mind, our recent strategy in CF patients is the use of polyvalent anti-lymphocyte serum to bridle the activated and up-regulated immune system of this special transplant population for prevention of acute rejection episodes within the first months and avoidance of disastrous infectious complications caused by multi- or pan-resistant bacteria. Unexpectedly, the type of pretransplant bacterial colonization had no influence on survival rates and was the same in both study arms (Table 1).

A closer look at the impact of ATG on rejection after LuTX reveals differentiated results: whereas the freedom from rejection showed only a strong trend towards a beneficial effect in the ATG group, which never reached statistical significance, the A scores were significantly lower. We have specifically placed the emphasis on the A scores, as we feel that this is a more clinically sensitive parameter when it comes to immunological activity.

However, all patients showed a good functional outcome following transplantation with a significant increase in FEV1 at 1-year following transplantation to almost 2.9 l (77% predicted) in both study groups as compared with preoperative values. Chronic rejection is common after the first year post-transplant, is characterized by obliterative bronchiolitis, and is found in up to 65% of 5-year survivors [15].

Freedom from BOS after 5 years was similar with 79% (group A) versus 80% (group B), an excellent result compared with the incidence of BOS documented in the ISHLT registry. Reason for the lower number of BOS in our patients could be the overall reduction of acute rejection episodes, one of the main risk factors for chronic allograft dysfunction and lower cumulative A scores after 100 days and 1 year.

The number of retransplantations was high, with an incidence of 7% in both study groups (Table 3).

Of course, there are some disadvantages of the increased immunosuppression: there was a trend towards a higher incidence of CMV infection/disease in the ATG group (not statistical significant) without having a negative impact on survival rates. The need for an effective CMV prophylaxis, especially in CMV mismatched patients, is obvious and has been the topic of multiple publications [16,17]. Of note, once again, with regard to bacterial infections, we observed a significant lower incidence in the more highly immunosuppressed population, a finding which seems to be counterintuitive.

Post-transplant lymphoma is the most common malignancy in lung transplantation, occurring in approximately 5% of lung transplant recipients [18]. The incidence of PTLD is higher in recipients receiving more aggressive immunosuppressive therapy [19], especially after use of ATG as induction or rescue agent [20]. In our cohort, the percentage of patients who developed PTLD was similar in both groups ($n = 3$ in ATG vs. $n = 1$, $P =$ ns). More importantly, we have not lost a single patient to PTLD.

We recognize that our study has several limitations, including the retrospective nature of the analysis of a single-centre experience. However, historical modifications in the management of lung transplantation (immunosuppressive regimen, different surgeons, organ procurement) have no impact on our results as demonstrated by the subgroup analyses of the different time periods. We did not have a selection bias, as patients received induction therapy irrespective of their pretransplant clinical status. It is important to note that induction therapy was initially administered in the context of clinical trials, accounting for a number of patients receiving no induction therapy. After a subgroup analysis performed in 2004, which revealed a significant survival benefit for patients receiving ATG induction, the majority of CF patients were induced henceforth. Moreover, even the findings of the multivariate regression promote our findings. ATG induction therapy and primary immunosuppression with tacrolimus were independent predictors for 90-day survival after LUTX. The stronger immunusupressive

capacity of Tacrolimus in comparison to cyclosporine might have additional beneficial effects to induction therapy. The current study is the largest series reported in the scientific literature examining the impact of ATG induction therapy in CF patients after lung transplantation.

Taken together, we conclude from our results that the use of ATG as an induction agent demonstrated excellent results with regard to survival and reduction of acute rejection compared with no induction therapy. A significant lower rate of deaths caused by infectious complications in the ATG group accounts for this improvement of survival. Induction therapy has always been discussed controversially in the literature; however, we feel that our report is a very strong indicator for a highly positive impact of this therapy in a particular subgroup of lung transplant recipients. Prospectively, randomized, multicentre trials are required to confirm our results and to establish valid guidelines for the immunosuppression management of this particular high-risk patient population.

Authorship

PJ, DW, AK and WK: participated in research design. PJ, VA, GM and AS: participated in collection of the data. PJ and DW: performed the statistical analysis. PJ, DW and AK: participated in writing of the manuscript. AK, WK, VA, GM and AS: participated in reviewing and correcting the manuscript. PJ, AK and DW: participated in manuscript preperation and submission.

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