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Basiliximab vs. Antithymocyte Globulin as Initial Induction Therapy for Lung Transplantation: A National Two Years Review

Bruno Mendes [1,*], Carlos Figueiredo [1], Mariana Cabral [1], Alexandra Borba [1], Alexandra Mineiro [1], João Cardoso [1], Paulo Calvinho [2], Luísa Semedo [1] and José Fragata [2]

[1] Serviço de Pneumologia do Hospital de Santa Marta, Centro Hospitalar Universitário de Lisboa Central, 1169-024 Lisbon, Portugal
[2] Serviço de Cirurgia Cardiotorácica do Hospital de Santa Marta, Centro Hospitalar Universitário de Lisboa Central, 1169-024 Lisbon, Portugal
* Correspondence: mendes.bruno@campus.ul.pt

Abstract: Basiliximab (BAS) is an interleukin-2 monoclonal antibody initially used as induction therapy after liver and kidney transplantation. BAS use after lung transplantation (LTx) has supplanted antithymocyte globulin (ATG) as the main induction immunosuppression over the years, but few studies have compared them. In this study, we aimed to compare the efficacy and safety between BAS and ATG in LTx. We performed a retrospective analysis of all LTx done in Portugal between January 2016 and December 2019. Three groups were made according to the initial induction status: BAS, ATG or no induction (NI). The occurrences of cytomegalovirus (CMV) infection, pneumonia, side effects, primary graft dysfunction (PGD), acute rejection, chronic allograft disfunction (CLAD) and death episodes were assessed during two years after LTx. A total of 124 patients were divided in 3 groups: 61 (49.2%) BAS; 43 (34.7%) ATG; 20 (16.1%) NI. The incidences of pneumonia and CMV were similar between induction groups. Additionally, there was no difference between the induction groups in PGD, acute rejection, CLAD, deaths and two-year survival. Side effects were reported only in ATG group (n = 20; 46.5%). In our study, BAS had a better safety profile than ATG in LTx with a similar efficacy.

Keywords: lung; transplantation; basiliximab; antithymocyte globulin; induction

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1. Introduction

In patients with end-stage lung disease, lung transplantation (LTx) can be a life-saving procedure [1,2]. Chronic lung allograft disfunction (CLAD) and infection are big limitations to survival after LTx [3]. The 5-year survival after LTx, conditional on surviving to the first year, varies between 62% and 75% [4]. The immune response is modulated by two immunosuppressive regimens: induction and maintenance therapy. There is no consensus about the necessity of induction therapy or the best drug to use [5,6]. Most lung transplant centres use induction therapy with polyclonal antibody preparations (equine or rabbit antithymocyte globulin (ATG)), alemtuzumab or an interleukin 2 receptor antagonist (IL2RA) such as Basiliximab (BAS). These agents may present with several adverse effects, such as drug toxicity and opportunistic infections [1]. ATG is the second most used induction agent for LTx. ATG is a polyclonal antibody preparation isolated from either rabbit or horse sera, which contain antibodies toward human thymocytes and cause significant T cell depletion [5,6]. Adverse effects associated with ATG include hemodynamic instability, fever, chills, rash, arthralgia, diarrhoea, leukopenia and thrombocytopenia [1]. BAS, the main induction agent used for LTx, is a monoclonal antibody that binds specifically to the α-subunit of the human high-affinity interleukin-2 receptor complex, consequently inhibiting interleukin-2 (IL-2) binding. IL-2 receptors are selectively expressed on the surface of the activated lymphocytes. Administration of BAS inhibits the IL-2-mediated activation of lymphocytes, a critical pathway involved in allograft rejection. Although

experience with BAS in LTx is limited, it has shown its efficacy in the control of acute rejection in other organ transplant recipients, accompanied by an excellent safety profile in terms of adverse effects [7,8].

Although studies showed that induction with ATG or IL2RA reduced the incidence of primary graft dysfunction (PGD) and CLAD, a comparison between these two agents has shown inconclusive results as far as PGD, CLAD, infection, safety and survival rates are concerned [1,6,9–12].

The objective of our work was to compare the efficacy and safety between BAS and ATG as the main induction therapy in LTx.

2. Material and Methods

2.1. Study Design

We performed a retrospective analysis of all LTx done in our Centre of LTx between March 2016 and December 2019.The primary end points of the study were to compare the incidence of PGD, acute rejection, CLAD and infections between three groups (according to the induction immunosuppression status: BAS, ATG or no induction (NI)). In addition, we compared patients' tolerance to BAS and ATG and the incidence of bacterial, fungal and CMV infections. The two years' cumulative survival after LTx was also compared between these three groups. The project does not include any interaction or intervention with human subjects, and the research activities were consistent with the Principles of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

2.2. Data Collection and Definitions

Electronic medical records of all transplanted patients during the study period were accessed. Three groups were made, according to the induction immunosuppression status: BAS, ATG or NI. The induction agent of choice varied depending on the time of transplantation (BAS started to be used in our centre in February 2018 instead of ATG). Rabbit ATG was administered (10 mg/kg) once after 100 mg intravenous (IV) hydrocortisone, 2 mg IV clemastine and 1000 mg IV paracetamol 24 h after LTx. Due to reported adverse effects related to ATG, before February 2018, patients who were clinically unstable in the first 24 h after LTx did not receive induction therapy. Medical instability was defined as the presence of at least one of the following, despite optimal treatment: Hypotension (systolic blood pressure < 80 mmHg), hypertension (systolic blood pressure > 140 mmHg), hyperthermia (>38 °C) or partial pressure of oxygen to fraction of inspired oxygen $\leq$ 300 mmHg with positive end-expiratory pressure or continuous positive airway pressure $\geq$ 5 cm H_2O. BAS was given (20 mg infusion) immediately following lung transplantation and on post-operative day 4. Dosages of immunosuppressive maintenance drugs were similar between groups and consisted of a three-drugs strategy, with a cell-cycle inhibitor (mychophenolate mofetil or azathioprine), a calcineurin inhibitor (tacrolimus preferred), an mTOR inhibitor (everolimus preferred) and corticosteroids.

PGD was defined according to the Society for Heart and Lung Transplantation (ISHLT) as acute lung injury characterized by diffuse alveolar infiltrates on chest X-ray imaging, with associated hypoxemia, in the first 72 h after release of the second lung recipient pulmonary arterial cross-clamp [13]. Surveillance bronchoscopy with transbronchial biopsy was performed every month for the first three months, again six months after transplantation and when there was clinical indication. Acute rejection was defined as histological evidence of the presence of perivascular and interstitial mononuclear cell infiltrates in transbronchial biopsy, and A2 or higher grading [14,15] were treated following guidelines and our hospital policy. The acute rejection B scores were not evaluated in this study because of the wide variability in B grading. CLAD was diagnosed according to the ISHLT definition as a substantial and persistent decline ($\geq$20%), over three weeks, in a measured Forced Expiratory Value in the first second (FEV1) value from the reference (baseline) value, which was not explained by other causes. The baseline value was defined as the mean of the best two post-operative FEV1 measurements taken three or more weeks apart [3]. All

patients routinely follow-up spirometry at our laboratory, at least four times per year, in the first two years after LTx. if pneumonia was suspected, sputum cultures were collected. Pneumonia was defined clinically by the presence of respiratory symptoms (fever, dyspnea, thacypnea or cough), laboratory abnormalities (leucocytosis or leukopenia) and radiologic evidence of an airspace disease on computed tomography.

In cases where donors (D) and/or the receptor (R) were CMV IgG-positive, prophylaxis was given with intravenous ganciclovir (5 mg/kg every 12 h for 15 days), followed by oral valganciclovir (450 mg every 12 h for 6 months if R+/D− or R+/D+ and 12 months if R−/D+). In R−/D+ cases, Cytomegalovirus immune globulin was also administered as an adjunct for 12 months. Patients were tested weekly through a blood sample for CMV during their recovery in the ward after LTx. After discharge, blood surveillance for CMV infection was done every three months.

CMV infection in a lung transplant recipient could present as asymptomatic viremia or CMV disease (manifested as a viral syndrome or as a tissue-invasive disease, mainly pneumonitis). As the clinical features of CMV disease are nonspecific, we only assessed the presence of CMV infection, defined as the detection of a positive viral load in R−/D+ cases or a polymerase chain reaction test $\geq$ 4000 copies/mL of DNA if R+.

2.3. Statistical Analysis

The occurrence of PGD, acute rejection, CLAD, cytomegalovirus (CMV) infection, side effects, pneumonia and death were assessed during the first two years after LTx. The cumulative survival in two years between the three groups was also recorded. The results were analysed and compared with a chi-square test using IBM SPSS Statistics version 25© (Lisbon, Portugal) (for the chi-square test use, at least 80% of the expected frequencies exceeded 5 and all the expected frequencies exceeded 1). When the chi-square test demonstrated a significant difference between the three groups ($p < 0.05$), the chi-square test between each of the two groups was applied to determine a pair comparison. Survival was assessed with a Log Rank (Mantel-Cox) Kaplan-Meier curve. Categorical variables are presented as frequencies and percentages, and continuous variables as medians and interquartile ranges, since all had skewed distributions. All reported *p*-values are two-tailed, with a *p*-value < 0.05 indicating a statistical significance.

3. Results

3.1. Patient Population

A total of 124 patients (n = 124), among them two re-transplanted patients, were divided into three groups: 43 ATG (34.7%); 61 BAS (49.2%) and 20 NI group (16.1%). ATG and NI groups included patients that received an LTx between March 2016–February 2018 and the BAS group included patients that received an LTx between February 2018–December 2019. All transplants were performed at Hospital de Santa Marta, Centro Hospitalar Universitário de Lisboa Central, the only transplantation centre in Portugal. No patient was excluded from this study. As seen in Table 1, no baseline differences were found between the groups as far as age, gender and type of surgery were concerned. The main indication for LTx was chronic obstructive pulmonary disease (COPD), followed by idiopathic pulmonary fibrosis (IPF).

3.2. PGD, Acute Rejection and CLAD

There was no statistical difference in the PGD between the two induction groups: ATG (n = 5; 11.6%) and BAS (n = 10; 16.4%), p = 0.496. When comparing the induction groups with the NI group, there was a significant statistical difference in the incidence of PGD (n = 10; 50.0%), p = 0.001. A lung biopsy compatible with acute rejection was found in eight patients in the ATG group (18.6%), in nine patients in the BAS group (14.7%), and the NI group had three patients with a development of acute rejection (15.0%). There was no difference between the three groups, p = 0.861. Twelve patients had CLAD in the ATG group (27.9%), elevent patients had it in the BAS group (18.0%), and six patients had it in

the NI group (30.0%). Additionally, no difference was found between the three groups in the CLAD diagnosis, $p = 0.376$ (Figure 1).

Table 1. Baseline characteristics of the three groups. COPD—Chronic obstructive pulmonary disease; IPF—Idiopathic pulmonary fibrosis; IQ—Interquantile; CF—Cystic fibrosis; HP—Hypersensitivity pneumonitis; BC—Bronchiectasis; AATD—Alpha-1 antitrypsin deficiency.

	ATG (n = 43)	BAS (n = 61)	NI (n = 20)	p Value
Age, median [IQ]	52.0 [15]	52.0 [16]	52.5 [28]	0.767
Male sex, *n* (%)	27 (62.8%)	40 (65.6%)	15 (75.0%)	0.630
Bilateral, *n* (%)	29 (67.4%)	50 (82.0%)	16 (80.0%)	0.210
Indication for LTx, *n* (%)				
COPD	8 (18.6%)	18 (29.5%)	4 (20%)	
IPF	9 (20.9%)	5 (8.2%)	4 (20%)	
CF	6 (14.0%)	8 (13.1%)	3 (15%)	
HP	6 (14.0%)	8 (13.1%)	2 (10%)	
BC	4 (9.2%)	5 (8.2%)	6 (30%)	
AATD	4 (9.2%)	2 (3.3%)	1 (5%)	
Others	6 (14.0%)	15 (24.6%)	0	

	ATG (n = 43)	BAS (n = 61)	NI (n = 20)	p Value ATG vs. BAS
PGD, *n* (%)	5 (11.6%)	10 (16.4%)	10 (50.0%)	0.496
Acute rejection, *n* (%)	8 (18.6%)	9 (14.7%)	3 (15.0%)	0.601
CLAD in 2 years, *n* (%)	12 (27.9%)	11 (18.0%)	6 (30.0%)	0.232

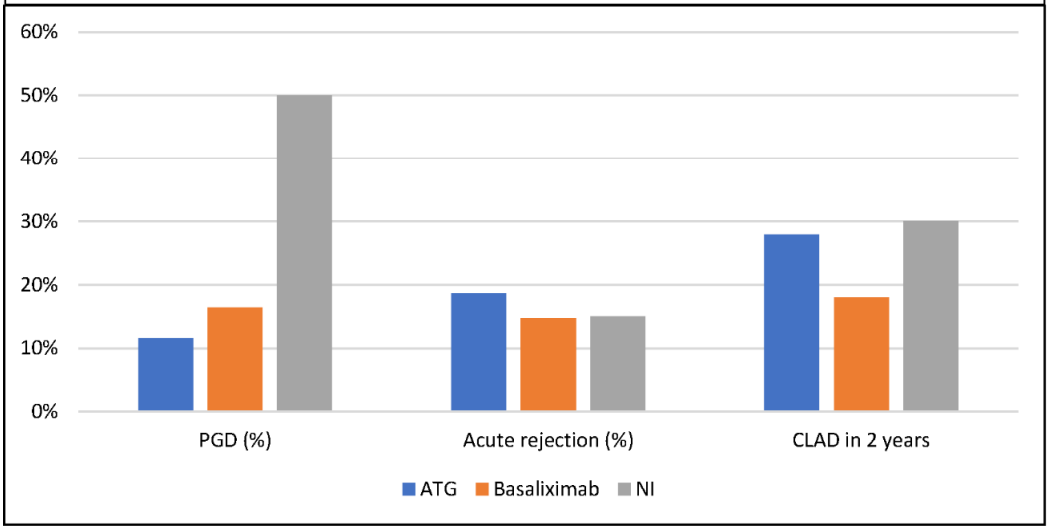

Figure 1. Comparison between PGD, acute rejections and CLAD events during 2 years after lung transplantation according to different induction therapies. CLAD—Chronic lung allograft disfunction; NI—No induction; PGD—Primary graft disfunction.

3.3. Infection

CMV infection developed in 12 patients in the ATG group (27.9%) and in 11 patients in the BAS group (18.0%), $p = 0.232$. In the NI group, one patient developed CMV infection (5.0%) (ATG vs. NI $p = 0.036$ and BAS vs. NI $p = 0.155$). In total, 87 out of 124 patients (70.1%) developed pneumonia: 31 in the ATG group (72.1%), 41 in the BAS group (67.2%) and 15 in the NI group (75.0%), $p = 0.757$. The cumulative incidence of a fungal pathological agent isolation in bronchoalveolar lavage cultures was 22 (5 ATG, 11 BAS, 6 NI groups; $p = 0.207$), and in bacterial organisms it was 86 (31 ATG, 39 BAS, 16 NI groups; $p = 0.265$) (Table 2). In fouir patients (two ATG and two BAS group), there was no identification of an

organism in the bronchoalveolar lavage culture, and pneumonia was diagnosed based on clinical and radiological evidence.

Table 2. Number of patients that developed cytomegalovirus (CMV) infection or pneumonia, and incidence of pathological agents identified in bronchoalveolar lavage. The cumulative number of events was not evaluated. ESBL+: Extended-spectrum β-lactamases; KPC: Klebsiella pneumoniae carbapenemase; MRSA: methicillin-resistant Staphylococcus aureus; MSSA: methicillin-susceptible Staphylococcus aureus.

	ATG (*n* = 43)	**BAS (*n* =6 1)**	**NI (*n* = 20)**	***p* Value ATG vs. BAS**
CMV infection, no (%)	12 (27.9%)	11 (18.0%)	1 (5.0%)	0.232
Pneumonia, no (%)	31 (72.1%)	41 (67.2%)	15 (75.0%)	0.595
Pathological agent				
Achromobacter Xylosoxidans		1		
Acinetobacter Baumanii		1		
Aspergillus Falvus		1		
Aspergillus Fumigatus	2	2		
Aspergillus Niger	1	1		
Aspergillus Terreus		1		
Burkholeria Cepacia	1			
Candida Albicans	1	4	3	
Candida Lusitaniae			1	
Candida Prapsilosis			1	
Candida Tropicalis			1	
Candida Krusei	1			
Citrobacter Koseri	1			
Enterobacter Aerogenes	2	1		
Enterobacter Clocae		2		
Haemophilus influenzae			1	
Influenzae	1			
Klebsiella ESBL+	1	2	1	
Klebsiella Oxytoca	1	1	1	
Klebsiella OXA 48				
Klebsiella Pneumoniae	2	8	3	
KPC	1	1		
Moraxella Catarrhalis		1		
Morganella Morganii		1		
MRSA	2	3		
MSSA	4	3	2	
Mycobacterium Tuberculosis		1	1	
Pneumocystis Jirovecii		2		
Proteus Mirabilis		1		
Pseudomonas Aeruginosas	10	11	5	
Serratia Marescens	2			
Streptococcus Pneumoniae		1	1	
Staphylococcus Epidermidis			1	
Staphylococcus Haemolyticus	1			
Stenotrophormonas Maltophilia	3	1	1	

3.4. Side Effects and Death

No side effects were observed in the BAS group, while 20 patients in the ATG group (46.5%) experienced side effects, $p = 0.000$. Hypotension was the most common adverse reaction, with 12 cases (60%), followed by hyperthermia ($n = 8$, 40%), agitation ($n = 6$, 30%), tachycardia ($n = 4$, 20%), hypertension ($n = 3$, 15%), tremors ($n = 2$, 10%) and nausea ($n = 1$, 5%). Death related to LTx complications occurred in eight patients in the ATG group (18.6%), 10 in the BAS group (16.4%) and 9 in the NI group (45.0%), $p = 0.022$, with no difference between the induction groups, $p = 0.769$. The cumulative survival at two years after LTx was 83% in the induction groups and 55% in the NI group, $p = 0.014$ (Figure 2).

Two patients died of other causes not related to LTx, one in the ATG (gastric cancer) and one in the BAS group (unknown cause), and they were not included in this analysis.

	ATG (n = 43)	BAS (n = 61)	NI (n = 20)	p Value ATG vs. BAS
Deaths, no (%)	8 (18.6%)	10 (16.4%)	9 (45.0%)	0.769
Side effects, no (%)	20 (46.5%)	0	-	0.000
Hypotension	12 (60.0%)	-	-	
Hyperthermia	8 (40.0%)	-	-	
Agitation	6 (30.0%)	-	-	
Tachycardia	4 (20.0%)	-	-	
Hypertension	3 (15.0%)	-	-	
Tremors	2 (10.0%)	-	-	
Nausea	1 (5.00%)	-	-	

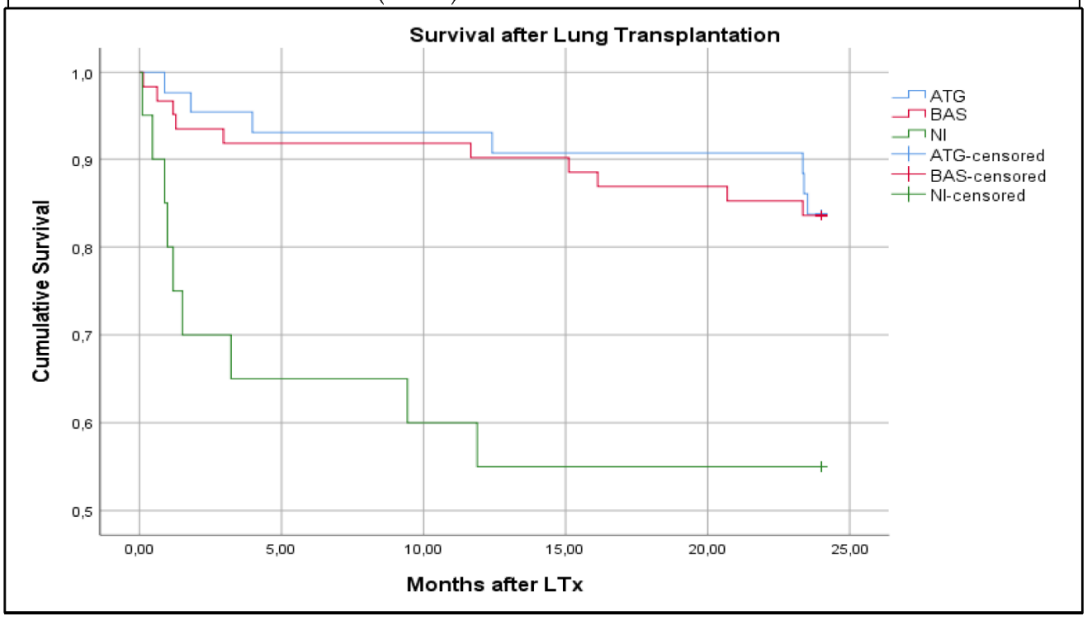

Figure 2. Comparison of deaths, patients with side effects reported after induction and survival after lung transplantation between the three groups.

4. Discussion

In this study, we compared the safety and efficacy of two induction regimens with BAS versus ATG in a cohort of patients receiving lung transplantation at our institution. We also assessed the data for an NI group, both as a control group and in order to describe outcomes. There were no differences in the baseline characteristics between the three groups.

In contrast to other studies that demonstrated a higher cumulative acute rejection with BAS when compared to ATG [6], our retrospective analysis showed that there was no difference in PGD, acute rejection or CLAD between the two induction groups. Our data also reinforces the importance of an appropriate initial induction, as no initial induction therapy after LTx was associated with a higher risk of developing PGD. Multiple studies have already demonstrated that acute rejection is associated with CLAD [15].

As far as infection is concerned, the NI group was associated with a lower incidence of CMV infection when compared with the two induction groups, with a statistic difference in relation to the ATG group. Between the two induction groups, the ATG one was associated with a higher incidence of CMV infection (27.9%) when compared to the BAS group (18%), although no statistic difference was found between them. These findings are consistent with a recent study published on renal transplant, which showed that low doses of ATG favoured the development of CMV and a lower survival free of CMV when compared with BAS [16]. Additionally, no difference was found between the number of patients who developed pneumonia between the three groups. It is important to note that the NI

group was formed by patients that were too unstable in the first 24 h after LTx to receive induction therapy, and therefore the clinical importance of the cumulative survival after two years (55%) is questionable. There was no difference in survival between the two induction groups.

A major finding in this study was the number of adverse reactions experienced in the ATG group (n = 20, 46.5%) when compared to the BAS group (n = 0). Hypotension was the most prevalent side effect, accounting for 60% of the cases.

There are some potential limitations to this study. The NI group's worse outcome and survival may be a consequence of the severity of the recipients at the time of transplantation. This low survival in the NI group may lead to an underestimation of the results of CLAD and infections for this group during this study. As a retrospective study, we assessed the side effects of induction according to documentation found in the electronic medical records. We acknowledge that some minor adverse effects may have occurred after BAS induction, but clinical effects were negligible and not recorded in the clinical process.

5. Conclusions

The present study indicates that BAS is a safe and efficient alternative to ATG as an induction therapy after LTx. There was no difference in PGD, acute rejection, CLAD, infection rate, death or cumulative survival in these groups of patients after induction with BAS or ATG. Our study showed no side effects from BAS induction, as opposed to almost 50% reported in the ATG group. A prospective study comparing these two induction regimens is needed to confirm our finding.

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