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Early Sirolimus-Based Immunosuppression is Safe for Lung Transplantation Patients: Retrospective, Single Arm, Exploratory Study

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Background: Sirolimus, a mechanistic target of sirolimus inhibitor, is an immunosuppression medication for patients undergoing heart and abdominal transplantation. Sirolimus-based immunosuppression administered *de novo* post-lung transplantation is associated with bronchial anastomosis healing-related complications. We hypothesized that sirolimus administration within the first postoperative month in selected lung transplant recipients is safe and may be associated with favorable short-term and long-term outcomes due to its anti-proliferative properties and minimal adverse side effects.

Material/Methods: Thirteen patients (13.3%; mean age, 46.8±11.9 years) received early sirolimus-based immunosuppression along with cyclosporine and prednisone; 10 patients received single-lung transplantation, 3 received double-lung transplantation, and all received induction immunosuppressants. Patients received early sirolimus-based immunosuppression after an uncomplicated postoperative course and detailed bronchoscopic assessment.

Results: Sirolimus was begun on a mean of 20.6±4.7 days postoperatively (range, 14–32 days). The in-hospital and 30-day mortality rate was 0%. At long-term follow-up, 5 patients died (due to bacterial infection in 4 patients and pneumocystis jiroveci pneumonia in 1 patient). The mean overall survival was 4.4±2.53 (range, 0.8–10.0) years, 1-year survival was 92%, and 5-year survival was 62%. In 4 patients (30.8%), sirolimus was stopped due to infection in 3 patients and re-transplantation in 1 patient. Only one of the 13 patients developed bronchiolitis obliterans syndrome. In patients still taking sirolimus, renal function, systolic blood pressure, and lipid profile were within normal ranges; however, these patients required statin therapy.

Conclusions: In selected lung transplant recipients, early sirolimus-based immunosuppression is safe and associated with beneficial short-term and long-term outcomes.

MeSH Keywords: **Immunosuppression • Lung Transplantation • Organ Transplantation • Sirolimus • TOR Serine-Threonine Kinases**

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Background

The early and late results of lung transplantation (LTx) are constantly improving. Early acute rejection (AR) episodes are prognostic and have been implicated in the development of chronic rejection, which is termed chronic lung allograft dysfunction (BOS) [1]. The current immunosuppression regimen involves calcineurin inhibitors; however, they have a serious side effect profile that includes chronic renal insufficiency (with rates of 20–30%) that leads to worse long-term survival in LT recipients [2]. Sirolimus has an established immunosuppressive role in heart and abdominal transplantation patients [3,4]. Studies of other organs showed that calcineurin inhibitor use can be significantly reduced and patients can even be weaned off them with good results when m-tor inhibitors are used for treatment [5]. Importantly, sirolimus, when administered *de novo* after LTx, has been associated with an increased number of bronchial healing complications that lead to increased early mortality. Therefore, the US Food and Drug Administration (FDA) warns that sirolimus should not be administered *de novo* after LTx [5,6]. Regardless of its bronchial complications, sirolimus has been shown to reduce the number of AR episodes when it is administered *de novo* after LTx [5]. Reducing the number of AR episodes and eliminating medications that cause and contribute to long-term morbidity may significantly improve the long-term survival of LT recipients. We believe that sirolimus, when begun within the first postoperative month in selected LT recipients according to the standardized inclusion criteria, is safe and associated with favorable short-term and long-term outcomes due to its antiproliferative properties and minimal adverse side effects [7].

Immunosuppression with sirolimus as the primary immunosuppressant and implementation within the first month after LTx should be achieved with the least possible nephrotoxicity; should have antiviral, antitumor, and antifungal properties; and should have properties that may inhibit the development of bronchiolitis obliterans (BOS). We hypothesized that these 3 targets can be achieved by the early (within the first month) administration of sirolimus-based immunosuppression in appropriately selected LT recipients. Therefore, this study aimed to evaluate the safety of using sirolimus early in the postoperative period. The study was retrospective, single arm, exploratory in selected group of patients.

Material and Methods

Ethical considerations

The approval of the local ethics committee was obtained for this study (KNW/0022/KB229/17, the Bioethical Committee, Silesian University of Katowice). Due to the retrospective nature of this study, the need to obtain informed consent was waived.

Patients

We reviewed cases of patients who received early sirolimus-based immunosuppression. We did not perform a comparative study because of major heterogeneity between the eventually studied groups (patients with uncomplicated follow-up versus those with complications during follow-up). From December 2004 to November 2014, 98 LTx procedures were performed at the Zabrze Lung Transplant Program at the Silesian Centre for Heart Disease in Zabrze, Poland. Thirteen patients (13.3%) with a mean age of 46.8±11.9 years were selected to undergo an early sirolimus-based immunosuppression regimen.

Early sirolimus administration was defined as administration within the first 30 days post-transplantation. Ten patients received single LTx, 3 patients received double LTx, and all patients received induction immunosuppression. Patients were selected to receive early sirolimus if they had an uncomplicated postoperative course and were decisively selected after undergoing a detailed bronchoscopic assessment.

Inclusion and exclusion criteria

Patients were administered early sirolimus if they had: uncomplicated healing of bronchial anastomosis after a detailed bronchoscopic assessment until the 14th postoperative day (POD), an uncomplicated intraoperative and early postoperative course, and no primary graft dysfunction.

The exclusion criterion for early sirolimus administration was the presence of any healing complications other than bronchial (e.g., prolonged air leaks or wound healing complications).

Drug administration

Each consecutive patient with LTx with an uncomplicated intraoperative course was assessed 72 hours postoperatively to see if early sirolimus could be administered. At our institution, the standard protocol is to perform a bronchoscopic examination of bronchial anastomosis daily and before extubation. When early anastomotic healing is appropriate, patients are flagged as candidates for early sirolimus-based immunosuppression. Then, on approximately days 10–14 and before days 28–30, a decisive bronchoscopic examination is performed to determine if an LTx patient should receive early sirolimus-based immunosuppression. Our bronchoscopic examination consists of assessing the bronchial anastomosis using the Couraud Grading System. Only patients with grade 1 anastomosis (complete, circumferential, primary mucosal healing) were accepted as candidates for sirolimus [8]. When an LTx patient is indicated to undergo sirolimus-based immunosuppression, sirolimus is begun at 1 mg per day; the trough levels are checked daily. Then, the dose is augmented twice daily.

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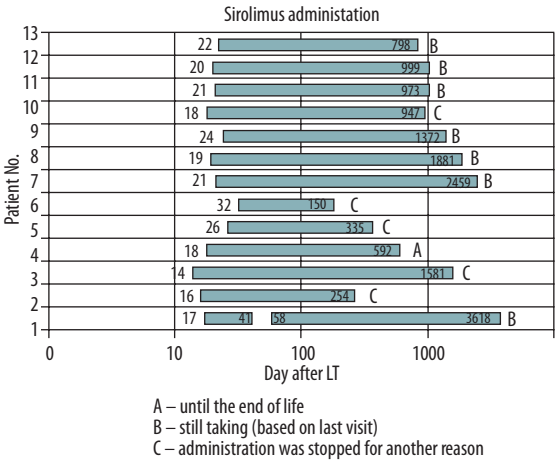

Figure 1. Initiation and duration of sirolimus administration. LTx–lung transplantation.

The initiation and duration of sirolimus administration are presented in Figure 1. Because sirolimus was administered early in our protocol, we assumed that the trough level should be higher than that after kidney transplantation. Our goal sirolimus trough level was established as 8 to 12 ng/mL. The targeted cyclosporine trough level should be 300 ng/mL (the routine dose after LTx) and should be achieved within 10 PODs, starting at 25 mg twice daily orally.

When sirolimus was begun, mycophenolate mofetil was immediately discontinued. A low dose of daily prednisolone was administered (5 mg/day). If the patient did not experience the side effects of this drug, our aforementioned regimen was maintained until 6 months postoperatively, after which our protocol calls for a slow reduction of cyclosporine to a level of approximately 150 ng/mL at the end of the first year after transplantation. Simultaneously, the sirolimus dose was raised to a target level of 10–14 ng/mL. After the first year, cyclosporine was slowly reduced over a period of 3 to 6 months to possibly discontinue the drug and start mycophenolate mofetil/azathioprine. Thus, the target long-term therapy in this regimen was combined sirolimus, mycophenolate mofetil, and prednisolone. Depending on the number of AR episodes and infections, further treatment was individualized. The appearance of nephrotoxicity at any given time resulted in a very rapid and large (50%) reduction in cyclosporine doses (100–150 ng in the first year after transplantation), with a mild increase in the target sirolimus level of 10–14 ng/mL.

Furthermore, when cyclosporine was discontinued, in a significant percentage of cases with long-term follow-up, mycophenolate mofetil was not restarted and patients were essentially maintained on 2-drug immunosuppression to have the fewest number of other-organ complications as possible. If a major surgical procedure was needed, patients were admitted as inpatients and transitioned to cyclosporine or tacrolimus. All elective surgical procedures were deferred for at least 3 months. After this time, patients could be transitioned back to sirolimus.

Because each patient undergoing LTx was considered a potential candidate for sirolimus therapy, the calcineurin inhibitor of choice was cyclosporine. We think that the combination of sirolimus and tacrolimus, which affect the same target protein (the FK 506 binding protein) might be unfavorable because of the competitive mechanism of these drugs.

Statistical analyses

The statistical analyses were performed with Microsoft® Office Excel 2000 (Microsoft Corporation) and Statistica 6.0 (StatSoft, Inc.). The distribution of the analyzed data was assessed using the Shapiro-Wilk test for normality. The differences between means were analyzed with Student's t-test, and in other cases, the non-parametric Mann-Whitney U significance test was used; P values of ≤ 0.05 were considered statistically significant. Data are presented as the mean ± standard deviation or median ± quartile deviation.

Results

Patients

The patient characteristics are summarized in Table 1. Sirolimus was begun on a mean POD of 20.6±4.7 (range, 14–32 days). The detailed results of all sirolimus levels that were achieved in patients who were treated with this drug are presented in Table 2. The in-hospital and 30-day mortality rate was 0%. No anastomosis dehiscence was observed in the study cohort. The detailed results regarding the cyclosporine levels are shown in Table 3.

On long-term follow-up, 5 patients died. The reasons for death included bacterial infection in 4 patients and pneumocystis jiroveci (PJP) infection in 1 patient. The post-transplantation results of patients who were treated with sirolimus are presented in Table 4.

The details of the deceased patients were as follows:

Patient number 2, Table 4

This patient died 0.82 years after undergoing LTx. She had a very smooth and uncomplicated postoperative and hospital course and was discharged home in very good condition.

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At home, she ceased preventive cotrimoxazol treatment due to nausea without conveying this information to the transplantation team. Eight months after transplantation, she was admitted on an emergency basis with of dyspnea. Transbronchial biopsy was performed and showed a massive number of PJP. Despite undergoing maximal therapy, the patient died.

Patient number 3, Table 4

This patient died 5.42 years after undergoing LTx. After having an uncomplicated follow-up course, this patient had some social status problems as well as poor compliance and problems that were reported too late. The patient suffered from

Table 1. Characteristics of sirolimus-administered patients.

Patient No.	1	2	3	4	5	6
Age* (years)	54.7	47.5	44.5	58.9	46.6	29.5
Sex	M	F	M	M	M	F
BMI* (kg/m^2)	27.7	21	20.4	21.2	16.0	19
Diagnosis	IPF	IPF	IPF	COPD	ILD	BO
Days of being on the waiting list	1	161	297	633	407	393
Diabetes before LTx	Yes	No	No	No	No	No
Hypertension before LTx	No	Yes	No	No	Yes	No
Cr* (µmol/L)	79	50	64	79	32	90
GFR* (mL/min/1.73 m^2)	112.4	108	101.4	93.5	273.8	68.2
Hypercholesterolemia before LTx	No	Yes	No	Yes	No	Yes
LTx type	SLT	SLT	SLT	SLT	SLT	SLT+reLT
Duration of mechanical ventilation (hours)	54	11	33	27	22	35
CPB time (min)	136	N/A	312	N/A	N/A	N/A
ICU length of stay (days)	4	10	7	10	5	4
Induction agent	ATG	ATG	ATG +Basiliximab	ATG +Basiliximab	ATG	ATG
Hospital length of stay (days)	77	38	35	33	66	59
Other immunosuppressive drugs	CSA, MMF, Prednisolone	MMF, Prednisolone	CSA	CSA, MMF, Prednisolone	CSA. MMF. Prednisolone	CSA, MMF, Prednisolone
Postoperative day of starting sirolimus	17	16	14	18	26	32
Postoperative day of stopping sirolimus and reason	Still taking from 41 to 58 days because of groin healing complications	254 days; Acute rejection, PCP	1,581 days	Took until the end of life	335 days; general surgery procedure	150 days; reLT, pneumonia due to immuno-suppression

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Table 1 continued. Characteristics of sirolimus-administered patients.

Patient No.	7	8	9	10	11	12	13
Age* (years)	24.8	45.1	59.5	57.1	41.6	17.9	49.3
Sex	F	M	F	M	M	M	M
BMI* (kg/m^2)	17.7	20.0	26.3	23.2	26.7	17.8	17.7
Diagnosis	iPAH	COPD	LAM	COPD	COPD	CF	CF
Days of being on the waiting list	290	582	932	96	1	64	489
Diabetes before LTx	No	No	No	No	No	Yes	Yes
Hypertension before LTx	No	No	Yes	Yes	No	No	No
Cr* (µmol/L)	82	93	67	95	97	44	71
GFR* (mL/min/1.73 m^2)	78.7	81.35	82.50	75.8	105.0	232.5	109.0
Hypercholesterolemia before LTx	No	No	Yes	No	Yes	No	No
LTx type	SLT	DLT	SLT	SLT	SLT	DLT	DLT
Duration of mechanical ventilation (hours)	49	20	12	20	11	10	16
CPB time (min)	190	N/A	N/A	N/A	N/A	N/A	N/A
ICU length of stay (days)	17	8	5	3	5	4	2
Induction agent	ATG	ATG +Basiliximab	ATG	Basiliximab	Basiliximab	Basiliximab	ATG
Hospital length of stay (days)	74	100	50	42	48	41	44
Other immunosuppressive drugs	CSA, MMF	CSA, MMF, Predni-solone	MMF, Predni-solone	MMF, Predni-solone	CSA, MMF	CSA, Predni-solone	CSA, MMF
Postoperative day of starting sirolimus	21	19	24	18	21	20	22
Postoperative day of stopping sirolimus and reason	Still taking	Still taking	Still taking	947 days; Operation: volume lung reduction surgery – native lung hyperi-nflation syndrome	Still taking	Still taking	Still taking

* At LTx day; CBP – cardiopulmonary bypass; ICU – intensive care unit; IPF – idiopathic pulmonary fibrosis; LAM – lymphangioleiomyomatosis; ILD – interstitial lung disease; iPAH – idiopathic pulmonary arterial hypertension; COPD – chronic obstructive pulmonary disease; BO – bronchiolitis obliterans; CF – cystic fibrosis; SLT – single lung transplant; DLT – double lung transplant; reLT – lung retransplantation; N/A – not applicable; ATG – anti-thymocyte globulin; POD – postoperative day; CSA – cyclosporin; MMF – mycophenolate mofetil.

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Table 2. Average sirolimus levels obtained from all measurements in all sirolimus-administered patients after transplantation.

Patient No.	Mean/median	SD/quartille deviation	Minimum	Maximum
1	11*	2.85	4.3	28.7
2	8.4	5.22	1	18.2
3	12.3*	8.75	2.9	30
4	10.7*	3.30	3.6	27.5
5	13.6	6.48	2.5	28.7
6	12.9*	6.23	2.5	30
7	14.7*	3.75	2.5	30
8	12.9*	4.43	2.9	46.6
9	30.0*	2.35	6.1	31.7
10	12.7	3.76	3.19	20.1
11	13.6	4.46	6.1	25.3
12	14.1	4.06	3.35	27.5
13	10.0	4.06	2	17.8
Average	13.6		3.3	27.9
SD	5.24		1.47	7.32

SD – standard deviation. * Median ± quartille deviation.

Table 3. Average Cyclosporin levels obtained from all measurements during the simultaneous administration of sirolimus after transplantation.

Patient No.	Mean/median	SD/quartille deviation	Minimum	Maximum
1	122.5*	45.74	37.4	308.9
2	250.3	92.16	110.2	415.7
3	163.65*	62.34	22.7	331
4	232.1*	128.90	37.7	855.4
5	290.9*	84.86	118	809
6	267.4*	114.55	25.3	798.6
7	200.6*	119.13	23.9	1570
8	262.2*	88.14	89.4	847.2
9	174.3*	49.80	5.3	396.6
10	247.5*	91.03	21.7	320.2
11	172.7	88.59	50.1	349.9
12	156.7*	51.83	20.7	531.9
13	202.4	117.38	14.5	470.6
Average	211.0		44.4	615.8
SD	51.26		37.25	358.44

SD – standard deviation. * Median ± quartille deviation.

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Table 4. Post-transplantation results (based on the last visit or last measurement during sirolimus administration) of sirolimus-administered patients.

Patient No.	Acute rejection <1 year	Acute rejection >1 year	Diabetes	Hypertension	Dislipidemic	Statin use	Cr (μmol/L)	GFR (mL/min /1.73 m²)	PJP	CMV Disease	In-hospital/ 30-day mortality	Mortality	Survival (year)	Best FEV1	FEV1 (% of best)	BOS
1	Yes	No	Yes	Yes	Yes	Yes	128	75.62	Yes	No	No	No	10.01	1.85	1.63 (88)	0-p
2	Yes (1)	Yes (1)	Yes	Yes	Yes	No	118	66	Yes	No	No	Yes	0.82	1.33	1.3 (100)	0
3	No	No	Yes	Yes	Yes	Yes	119	59.8	Yes	No	No	Yes	5.42	1.75	1.43 (82)	0-p
4	No	No	Yes	Yes	Yes	Yes	193	32.93	No	Yes	No	Yes	1.62	3.35	3.20 (95)	0
5	Yes	No	No	Yes	Yes	No	103	71.73	Yes	No	No	No	7.00	1.87	1.87 (100)	0
6	No	No	No	No	No	No	93	65.75	Yes	No	No	Yes	4.53	1.15	0.95 (83)	0-p
7	No	No	No	No	Yes	Yes	70	91.62	No	Yes	No	No	6.75	3.55	3.51 (99)	0
8	Yes (1)	No	No	No	No	No	99	75	Yes	No	No	No	5.16	2.48	1.30 (52)	2
9	No	No	No	Yes	Yes	Yes	95	55.33	No	No	No	No	4.26	1.24	1.19 (96)	0
10	No	N/A	No	No	Yes	No	162	40.47	No	Yes	No	Yes	3.24	1.85	1.37 (74)	0-p
11	Yes (1)	No	No	No	Yes	Yes	150	47.26	No	No	No	No	2.76	2.89	2.68 (93)	0
12	No	No	No	No	No	Yes	81	132.03	No	No	No	No	2.74	3.54	3.32 (94)	0
13	No	No	Yes	No	Yes	Yes	209	31.39	Yes	No	No	No	2.41	2.92	2.82 (96)	0

Cr – creatinine; GFR – glomerular filtration rate; PJP – pneumocystis jiroveci; CMV – cytomegalovirus; FEV – forced expiratory volume.

sudden dyspnea about a month before admission to the hospital, experienced rapid graft damage, and died during the diagnostic process due to massive hemorrhage in the native lung.

Patient number 4, Table 4

This patient died 1.62 years after undergoing LTx. The patient had poor compliance; although he had the symptoms of advanced pneumonia, he refused any medical help. He reported his problems too late and suffered from severe bacterial pneumonia. The patient was treated in a local hospital and died from pneumonia-related respiratory insufficiency.

Patient number 6, Table 4

This patient died 4.53 years after undergoing LTx due to infection. Revision LTx was performed as a rescue therapy on POD 150 due to massive pneumonia with respiratory insufficiency as a result of central vascular catheter contamination.

Patient number 10, Table 4

This 57-year-old patient died 3.24 years after undergoing LTx. He had advanced chronic obstructive pulmonary disease that was treated with single left LTx. The early clinical and 2-year follow-up courses were uneventful. Then, the patient developed major expansion of the native lung that was treated with intrabronchial valves. The reason for death was bacterial infection of the transplanted lung.

Survival and complications

The mean overall probability of survival was 4.4±2.53 years (range, 0.8–10.0), the 1-year survival rate was 92%, and 5-year

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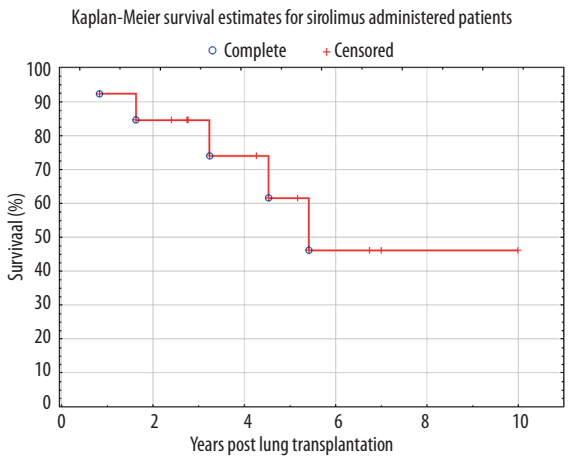

Figure 2. Kaplan-Meier survival estimation of patients who were treated with sirolimus.

survival rate was 62%. The Kaplan-Meier survival estimation of patients who were treated with sirolimus is presented in Figure 2. The survival of LT recipients who were treated with sirolimus did not differ from the survival of LT recipients who were treated without it.

In 4 patients (31%), sirolimus was stopped completely; 3 patients had infection and 1 patient was referred for re-transplantation. Due to our protocol, sirolimus was discontinued in 3 patients as our study target (Table 1).

The sirolimus trough level varied (minimum: 1 ng/mL and maximum: 30 ng/mL). The average value was 13.6 ng/mL in patients who continued to take cyclosporine. The average cyclosporine trough level was 211.0 ng/mL in patients who continued to take sirolimus.

Acute cellular rejection within the first year was diagnosed in 4 patients. Only 1 patient had an episode of acute cellular rejection after 1 year of observation (Table 4).

The creatinine values were statistically and significantly increased after transplantation during the study period, and the glomerular filtration rate (GFR) was decreased. There was a statistically significant difference in the creatinine level and GFR before and after transplantation during the study period: 73 µmoL/L versus 125 µmoL/L and 117 mL/min/1.73 m^2 versus 65 mL/min/1.73 m^2, respectively (Table 5).

The percentage of patients with diabetes increased during the studied period, from 23% to 38%, but not significantly (P>0.05). The percentage of patients with hypertension symptoms increased, from 31% to 46% (P>0.05) (Table 5).

There was a significant difference in patients with dyslipidemia before and after transplantation during the study period: 38% versus 77%, respectively (P<0.05) (Table 5).

Pre-emptive anti-cytomegalovirus treatment (based on a positive pp65 test) was necessary in 3 patients. Cotrimoxazol was administered in 7 patients based on the results of immunofluorescence sputum or a bronchoalveolar lavage study for the presence of PJP. This treatment was implemented as a preventative protocol, even if there were no symptoms of pneumonia or infection.

Only 1 of the 13 patients developed BOS-2 symptoms. Probable BOS (0-p) was observed in 4 patients. Bronchial complications appeared in 1 of the patients about 6 months after transplantation. These complications were judged as serious, and the patients were treated with stent implantation and frequent balloon bronchoplasty procedures. These consisted of the malacia distal to the anastomosis part of the bronchi.

Discussion

The main purpose of the study was to prove that sirolimus administered early and with specific criteria applied after lung transplantation is safe. As we have shown, administration of sirolimus as early as POD 15 in selected patients (without

Table 5. Mean values of parameters assessed before and after transplantation.

Parameter	Mean value pre-transplantation	Mean value post-transplantation*	p-Value
Creatinine [µmoL/L]	72.5±20.6	124.6±42.6	0.0008#
GFR [mL/min/1.73 m^2]	117.1±62.6	65.0±26.9	0.0049#
Diabetes	23% (n=3)	38% (n=5)	NS^
Hypertension	31% (n=4)	46% (n=6)	NS^
Hypercholesterolemia	38% (n=5)	77% (n=10)	0.0236^

GFR – glomerular filtration rate; * last visit; # student t-test; ^ the significance difference test between two proportions.

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complications postoperatively) was not associated with bronchial dehiscence.

Considering the current knowledge about the physiology of wound healing, in this study we rigorously adhered to a protocol to completely avoid non-healing of bronchial anastomosis. More specifically, we did not note any cases with bronchial anastomosis dehiscence, and no patients were at a risk of having such a complication.

There was no need to discontinue sirolimus in response to the suspicious appearance of bronchial healing after switching to therapy. Therefore, this finding is in contrast to the results of studies from 2 centers [5,6] that reviewed the background for the FDA's decision in which sirolimus "*de novo*" in lung transplantation was banned. The aforementioned publications were focused on how very early sirolimus would affect outcomes in lung transplantation patients. These studies were unique because they initiated sirolimus on POD 1; we feel that this was the driving, most important reason behind the higher incidence of bronchial dehiscence in those studies compared to our study. Moreover, our study considered the natural process of wound healing.

The most important aspect of wound healing which sirolimus may inhibit are: fibrocytes mobilization and migration, fibrocytes turn into fibroblasts, early angiogenesis within the wound, fibroblast production of fibrous collagen, production of required growth factors, and local healing mediators. These steps achieve their plateau around day 14. Knowing this, we decided to initiate sirolimus no earlier than POD 14. One of the basic principles of and expectations about the early implementation of sirolimus was the hope of better kidney protection [9,10]. However, in the group of patients who were analyzed in this study, there was a significant deterioration in renal function. The assessment was based on the analysis of the GFR and serum creatinine concentrations. At the end of the observation period, a statistically significant difference in the parameters was observed. After analyzing all the data, we postulated that we reduced the cyclosporine dose very slowly and late. This was due to the introduction of immunosuppression strategies. The expected nephroprotective effect may occur with decreased and shortened exposure to calcineurin inhibitors. This was a weak point of the study in terms of adhering to the sirolimus protocol.

Four patients in our study group experienced severe acute cellular rejection in the first year after transplantation, and 1 patient was diagnosed with AR beyond 1 year after transplantation. As the International Society for Heart and Lung Transplantation (ISHLT) data showed, these diagnoses are close to those of the general population of LT recipients [2]. Sirolimus administration does not show any advantages or disadvantages in this regard.

In our study group, there was an upward trend in the incidence of diabetes and hypertension during the long-term follow-up period. The increase in the incidence of both diabetes and hypertension did not differ from the data reported in the ISHLT reports [2] and it cannot be clearly stated that this increase was associated with the described immunosuppression protocol.

There was a significant increase in the number of patients with lipid abnormalities in our study group. However, the incidence of vascular complications was not increased. None of the patients had coronary artery disease or complications due to peripheral vascular disease.

The study protocol described for the use of "*de novo*" sirolimus in patients undergoing LTx appears to be safe regarding bronchial healing. The results of long-term observation in this small group of patients indicate a favorable trend in BOS-related outcomes which can be explained by the anti-proliferative effect of early treatment [11]. On the other hand, we must bear in mind that the undisturbed process of bronchial healing seen in patients before sirolimus introduction can also be a favorable anti-BOS factor. There was no nephroprotective effect of the protocol, possibly due to the inadequate, not dynamic enough, dose reduction of calcineurin inhibitors. During the long-term follow-up, the lipid and glucose profiles showed an unfavorable trend.

This study had some limitations. We could not use a comparative analysis because it was impossible to randomize the patients. Patients who had to be excluded from the study group based on bronchoscopic evaluation could not serve as the control group. In addition, the number of patients was small despite the long enrollment time. Our program started in December 2004 and was the only lung transplantation program in Poland. The number of transplantations per year was low at the beginning – mainly due to a very low number of patients directed to this treatment as it was very new at that time. After a few years, the situation had changed. The strict adherence to criteria which allowed us to enroll patients into early sirolimus immunosuppression was the reason only 13 patients were studied. Furthermore, in this retrospective analysis, we found that the cyclosporine tapering rate was not in accordance with the established protocol in which a lower level of the drug was postulated.

Conclusions

The study was retrospective, single arm, exploratory in a selected group of patients. Although the number of patients in our study was small, this is perhaps the largest group of its kind. The described protocol is safe for bronchial healing with strict adherence to the enrollment protocol, with the definition of

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early drug introduction being within first month. Therefore, for lung transplantation centers that are of the opinion that early modification of immunological response after transplantation may improve long-term results, especially the occurrence of BOS, our protocol could be a guide on how to identify patients who could be treated with "*de novo*" sirolimus. The promising BOS tendency that we report may be the impetus for a large prospective multicenter study that observes a significantly higher number of patients than that observed in our study.

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