

Original Article

## Pneumonitis associated with sirolimus: clinical characteristics, risk factors and outcome—a single-centre experience and review of the literature

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### Abstract

**Background.** The introduction of sirolimus as an immunosuppressive drug for renal transplantation has led to an increase of unexplained interstitial pneumonitis.

**Methods.** Out of a cohort of 115 patients receiving sirolimus for prophylaxis of renal and/or pancreas transplant rejection, 11 patients with interstitial pneumonitis were identified. Medical records and published case series were reviewed to identify risk factors associated with the occurrence of pneumonitis.

**Results.** Eleven out of 80 patients (14%) with late switch to sirolimus developed pneumonitis, in contrast to none of the 35 patients with *de novo* use of sirolimus. The mean sirolimus trough level at presentation was 16.7 µg/l (range: 6.2–38.7 µg/l). Glomerular filtration rate (GFR) was significantly lower in patients with pneumonitis compared to controls (mean 21.3 ± 3.9 ml/min vs 38.65 ± 2.14 ml/min  $P=0.002$ ). Two patients needed haemodialysis shortly before pneumonitis was diagnosed. In a multivariate analysis only serum creatinine and GFR were independent predictors for pneumonitis.

Sirolimus was discontinued in five patients and the dose reduced in the other patients. Pneumonitis resolved within 14–28 days in all patients. One patient who had continued low-dose sirolimus treatment relapsed after 5 months, the other five patients had no relapse over a period of 15–48 months.

Pooled analysis of our data and other published case series showed that the frequency of pneumonitis in patients with *de novo* use of sirolimus is significantly

lower than in patients with late switch [5/133 (4%) vs 46/326 (14%) patients,  $P=0.0024$ ].

**Conclusions.** Late switch to sirolimus and impaired renal function are risk factors for pneumonitis. A sirolimus blood trough level above 12 µg/l may increase the risk, but pneumonitis may also occur at blood trough levels as low as 6 µg/l. Since pneumonitis may recur during low-dose sirolimus treatment, discontinuation of sirolimus appears to be the safest treatment option.

**Keywords:** pancreas transplantation; pneumonitis; rapamycin; renal transplantation; risk factor; sirolimus

### Introduction

The introduction of sirolimus (rapamycin) as an immunosuppressive drug for renal transplantation has led to an increase of unexplained interstitial pneumonitis. A recent review reported 43 patients with sirolimus-induced pulmonary toxicity, observed after renal, liver, heart and heart-lung transplantation [1]. Diagnosis is made by exclusion of infective, auto-immune and toxic causes of lung injury. The pneumonitis responds to drug withdrawal, however, regression of pneumonitis is also described after dose reduction of sirolimus [2,3]. Factors that may be related to the risk for sirolimus-related pneumonitis may include late switch to sirolimus, age, underlying disease, concomitant immunosuppressive treatment and serum levels of sirolimus [3].

Here, we report 11 cases of suspected sirolimus-induced pneumonitis. The medical records of our patients and the literature were reviewed to assess the risk factors of this drug-induced pulmonary toxicity.

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**Table 1.** Characteristics of patients with sirolimus-associated pneumonitis

Patient	Age	Gender	Nephropathy	Time since RTx (months)	Immunosuppression	Onset of symptoms (months)
1	61	M	Hypertensive nephropathy	15	S,P (2 mg/day)	5
2	62	M	Chronic glomerulonephritis	108	S,P (7.5 mg/day)	8
3	34	F	Diabetic nephropathy	25	S,P (10 mg/day)	2
4	60	M	Polycystic kidney disease	11	S,P (5 mg/day)	4/9
5	61	F	Chronic interstitial nephritis	32	S,P (5 mg/day)	2
6	58	M	Analgesic nephropathy	42	S,P (5 mg/day)	3
7	47	M	IgA nephropathy	60	S,C,P (5 mg/day)	4
8	35	M	Diabetic nephropathy	55	S, P (10 mg/day)	1
9	68	F	Chronic pyelonephritis	37	S, P (5 mg/d)	1
10	44	M	Diabetic nephropathy	27	S, P (5 mg/day)	1
11	49	F	Chronic glomerulonephritis	21	S,FK,P (5 mg/day)	2

RTx, renal transplantation; S; sirolimus; FK, tacrolimus; C, ciclosporine A; P, prednisone.

Furthermore, we report our experience with dose reduction of sirolimus as a treatment option of pneumonitis in six patients.

## Methods

Medical records of patients from a single transplantation centre receiving sirolimus for prophylaxis of renal and/or pancreas transplant rejection were reviewed. Overall 115 patients were treated with sirolimus in our centre, 35 patients received low-dose sirolimus 2 mg/day in combination with tacrolimus ( $n=27$ ) and mycophenolate mofetil (MMF;  $n=6$ ) as first line prophylaxis of renal transplant rejection. Eighty patients were switched to sirolimus due to chronic transplant rejection or renal calcineurin inhibitor toxicity. Thirty-one patients had a combination treatment with tacrolimus, four patients with ciclosporine A and nine patients with MMF. Eighty-one patients underwent kidney transplantation, 33 patients had a combined kidney and pancreas transplantation and one patient had an isolated pancreas transplantation.

All patients with pneumonitis underwent computed tomography scans of the lungs. Bronchoalveolar lavage (BAL) was performed to exclude infectious agents, except in two patients due to anti-coagulation with cumarine and refusal to give informed consent. Medical records were reviewed and sirolimus trough levels measured by immunoassay to identify risk factors associated with the occurrence of pneumonitis. Glomerular filtration rate (GFR) was calculated by the modification of diet in renal disease (MDRD) formula according KDOQI.

We also reviewed all reports with more than one case report of sirolimus-associated lung toxicity to discuss the risk factors, treatment and outcome of pneumonitis.

Statistical methods included the Mann–Whitney rank sum test, chi-squared test and binary logistic regression to evaluate possible predictors for pneumonitis. The following biological parameters have been tested in univariate analyses: age, gender, sirolimus trough level, serum creatinine, GFR, proteinuria, time since transplantation, *de novo* use or late switch to sirolimus, immunosuppressants other than sirolimus and kidney disease. Multivariate analysis was used to validate whether possible predictors are related to pneumonitis independently from other biological parameters. *P*-values less than 0.05 were considered

statistically significant. We calculated the coefficients Exp (B) (equivalent-to-odds ratio) and their 95% confidence intervals (95% CI). All analyses were conducted with the use of SPSS (Chicago, IL, USA, Version 11.5.1).

## Results

Out of 115 patients receiving sirolimus, 11 patients (9.6%) with interstitial pneumonitis were indentified. The patient characteristics are summarized in Table 1. Nine patients received sirolimus in combination with low-dose prednisone (range 2–10 mg/day), one patient received a triple combination with sirolimus and tacrolimus and one patient combined with ciclosporine A and prednisone. None of the 35 patients with *de novo* use of sirolimus developed pneumonitis ( $P=0.02$  vs patients with pneumonitis, chi-squared test).

### Clinical presentation

The patients presented with low-grade fever ( $n=8$ ), dry cough ( $n=7$ ), dyspnoea on exertion ( $n=4$ ), fatigue ( $n=3$ ), and weight loss ( $n=2$ ), haemoptysis ( $n=1$ ) and chills ( $n=1$ ). Fever or weight loss was the sole symptom at presentation in three patients, whereas in the remaining eight patients pulmonary symptoms lead to the diagnosis of pneumonitis. Leucocyte counts varied markedly (mean 7433/ $\mu$ l, range 1100–12 000/ $\mu$ l and C-reactive protein levels were elevated (mean 11.1 mg/dl, range 1.1–23.5 mg/dl) (Table 2).

### Comparison of patients with and without pneumonitis

Male gender was equally distributed in both groups (64% of patients, respectively). The mean age was not significantly different in both groups [ $52.6 \pm 3.47$  years (SEM) vs  $47.5 \pm 1.33$  years (SEM) in patients with or without pneumonitis], as well as the kidney disease leading to end-stage renal disease. The mean sirolimus trough level at diagnosis of pneumonitis was 16.7  $\mu$ g/l (range: 6.2–38.7  $\mu$ g/l) (Table 2). However, the mean sirolimus trough levels within the first year after

**Table 2.** Laboratory findings in eleven patients with sirolimus-associated pneumonitis

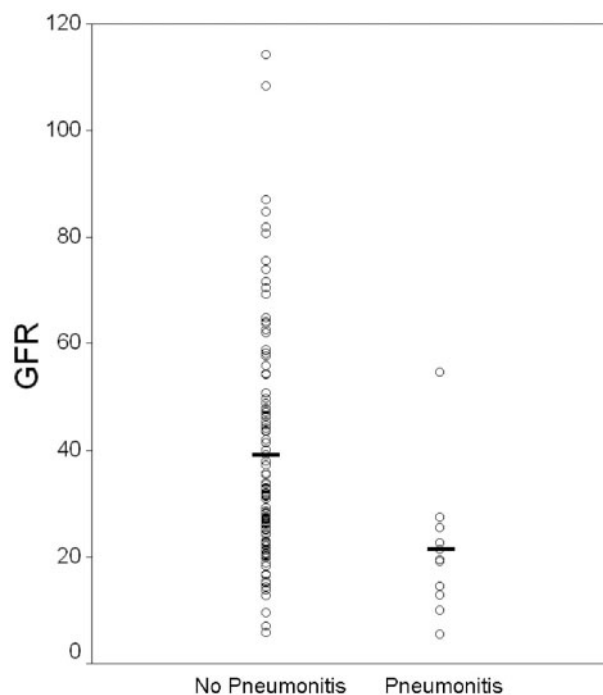
Patient	Leukocytes/ml	C-reactive protein (mg/dl)	Creatinine mg/dl	Sirolimus blood levels (µg/l)
1	5.100	8	3.0	16.8
2	9.700	3.1	4.6 (haemodialysis)	16
3	12.000	16	2.3	13.5
4	[1] 2.600 [2] 3.600	16.6 7.3	4.8 (haemodialysis) 4.8 (haemodialysis)	21 15.8
5	9.700	17.6	2.3	18.5
6	1.100	14	4.3	13.6
7	8.200	7.7	3.3	6.2
8	11.400	1.1	5.3	7.5
9	6.300	3.4	1.9	14.1
10	9.800	23.6	2.4	38.7
11	9.700	14.2	2.9	24.2

institution of sirolimus did not differ in patients with or without pneumonitis ( $9.75 \mu\text{g/l} \pm 3.57$  vs  $10.01 \mu\text{g/l} \pm 3.83$ ). Transplant renal function was severely impaired in all patients with pneumonitis (mean serum creatinine:  $3.1 \text{ mg/dl}$ , range:  $1.9$ – $5.3 \text{ mg/dl}$ ). Two patients needed haemodialysis shortly before pneumonitis was diagnosed. The mean GFR was significantly lower in patients with pneumonitis ( $21.3 \pm 3.9 \text{ ml/min SEM}$ ) compared with patients without pneumonitis ( $38.65 \pm 2.14 \text{ ml/min SEM}$ ),  $P=0.002$  (Mann–Whitney rank sum test) (Figure 1). Tacrolimus was significantly more frequently used in patients without pneumonitis ( $n=57$ ; 55%) vs patients with pneumonitis ( $n=1$ ; 9%) ( $P=0.01$ ). The other immunosuppressive drugs were not different in patients without and with pneumonitis: prednisone ( $n=98$ ; 94% vs  $n=11$ ; 100%), mycophenolate ( $n=16$ ; 15% vs  $n=0$ ), cyclosporine A ( $n=3$ ; 3% vs  $n=1$ ; 9%), azathioprine ( $n=1$ ; 1% vs  $n=0$ ),  $P=NS$  for all.

Univariate analysis (binary logistic regression) revealed serum creatinine [ $P=0.007$ ; Exp(B) (95% CI)= $1.738$  ( $1.165$ – $2.593$ )] and low GFR (MDRD) [ $P=0.011$ ; Exp(B) (95% CI)= $0.916$  ( $0.857$ – $0.980$ )] as significant predictors for pneumonitis. The risk of pneumonitis was significantly lower in patients using tacrolimus [ $P=0.02$ ; Exp(B) (95% CI)= $0.084$  ( $0.01$ – $0.68$ )]. Other parameters (age, gender, proteinuria, sirolimus trough levels, kidney disease, other immunosuppressants, *de novo* or late use of sirolimus) were not predictive for pneumonitis. Multivariate analysis showed that serum creatinine [ $P=0.014$ ; Exp(B) (95% CI)= $1.902$  ( $1.141$ – $3.170$ )] and GFR [ $P=0.020$ ; Exp(B) (95% CI)= $0.909$  ( $0.839$ – $0.985$ )] were predictive for pneumonitis independent of the other biological parameters tested, whereas the effect of tacrolimus was dependent of *de novo* use of sirolimus.

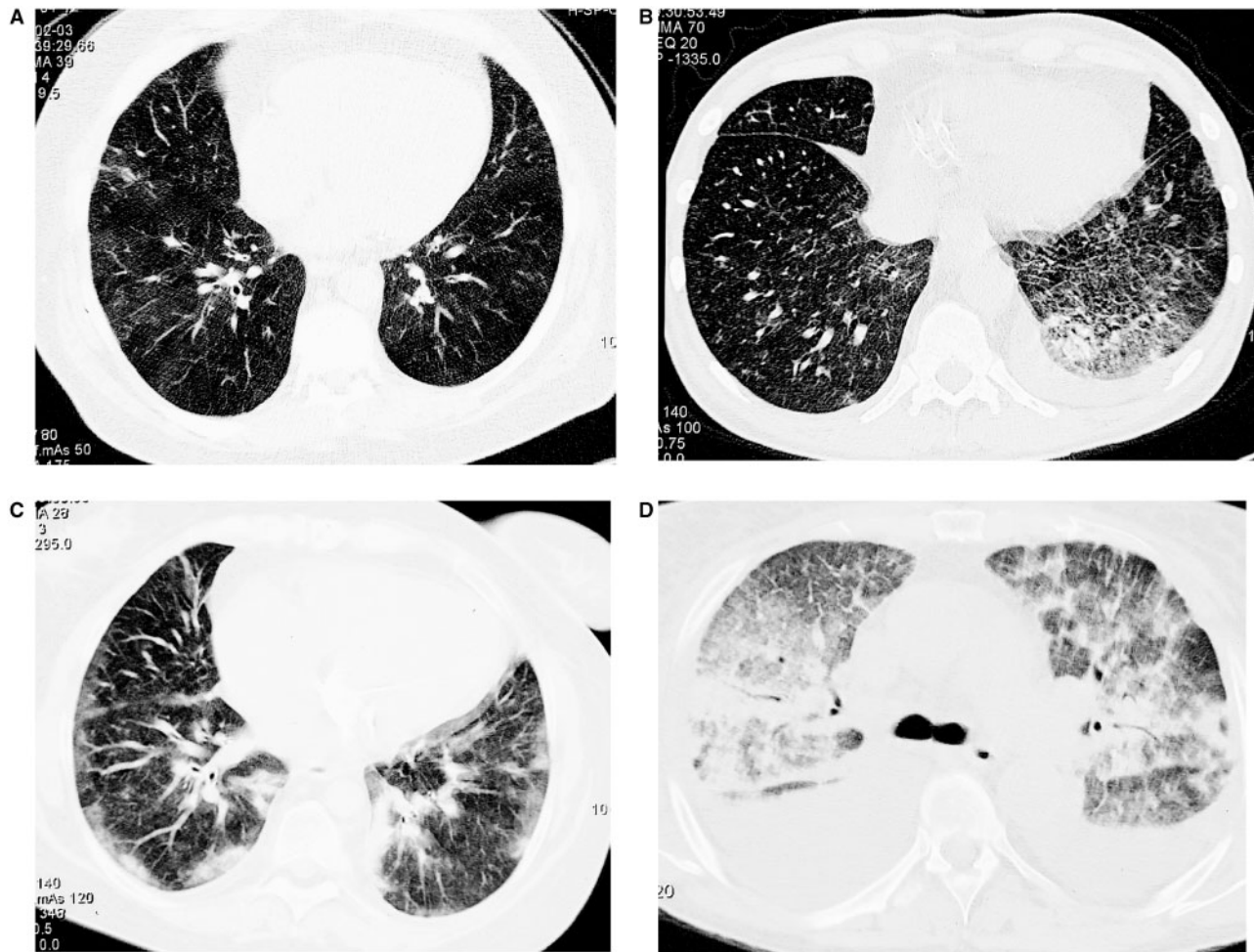
#### Lung imaging and bronchoalveolar lavage

Chest radiography was without pathological findings in four patients. CT scans of the lungs revealed bilateral mostly peripheral interstitial infiltrates in seven patients, accompanied with ground-glass



**Fig. 1.** Correlation between renal function at the time point of the start of sirolimus treatment and the occurrence of pneumonitis. GFR was calculated by the MDRD formula according to the KDOQI. The difference between patients suffering from pneumonitis and event-free patients with sirolimus medication was statistically significant (mean GFR  $\pm$  SEM:  $21.3 \pm 3.9 \text{ ml/min SEM}$  vs  $38.65 \pm 2.14 \text{ ml/min SEM}$ ;  $P=0.002$ , Mann–Whitney Rank sum test).

opacities in five patients. Four patients presented with ground-glass opacities only (Figure 2). BAL was performed in nine patients. Blood cultures and cultures obtained from bronchial aspirates were negative. Cells obtained from BAL were analysed in three patients, showing lymphocytic alveolitis in two patients (71% and 83% lymphocytes) with a CD4/CD8 ratio within normal range. One patient had alveolar haemorrhage in BAL analysis. In two out of eight patients, PCR detected sequences of *Mycoplasma pneumoniae* (patient 5), influenza virus A (patient 3) and



**Fig. 2.** High-resolution computed tomography studies of patients with sirolimus-associated pneumonitis. (A) and (B): Diffuse areas of ground-glass opacification, (C) and (D): Patchy areas of infiltrations in combination with areas of ground-glass opacities.

cytomegalovirus (CMV) (patient 3). Mycoplasma serology, blood CMV antigen (PP65) and CMV DNA repeatedly tested negative. Antibiotic and antiviral treatment did not lead to improvement of the condition in these two patients.

#### *Treatment and outcome*

Sirolimus was discontinued in five patients and the dose of sirolimus reduced in the remaining six patients. Antibiotic treatment was given in 10 of the 11 patients without an obvious benefit. Pneumonitis resolved within 14–28 days in all patients. Patient 4 continued sirolimus at a dose of 4 mg/day and a sirolimus blood level of 10 µg/l, but relapsed after 5 months. At this time, the sirolimus-level was elevated again (15.8 µg/l). After discontinuation of sirolimus pneumonitis regressed within 2 weeks. The remaining five patients with continued sirolimus medication had no relapse in the follow-up period of a mean of 29 months (range 15–48 months). The sirolimus dose was reduced to 1 mg/day in three patients, 3 mg and 6 mg in one patient, respectively. The mean sirolimus-level 1 month after

resolution of pneumonitis was 8.92 µg/l (range 7.9–10.5 µg/l) and was held in this range during the follow-up period.

#### **Discussion**

The frequency of interstitial pneumonitis appears to be increased in renal transplant patients receiving sirolimus. Our study shows a frequency of 11 cases with pneumonitis out of 115 patients exposed to this drug, consistent with the estimated frequency of 5–11% according to previous studies [3,4]. Table 3 summarizes the literature including case series with more than one reported case [1,3,5–10].

Pneumonitis developed within 1–8 months after initiation of sirolimus therapy in accordance with the literature with the onset of symptoms within 1 and 51 months [3].

The clinical presentation of sirolimus-induced pneumonitis is heterogenous; fever occurs in 73% of patients, dyspnoea and cough may be the leading symptoms in most patients [1–3]. In our case series,



In human experience, most individuals with pneumonitis had sirolimus trough concentrations ranging between 15 and 30 ng/ml [2,12,13]. These reports contrast with other case series of lower sirolimus trough concentrations: 8.3–11.2 ng/ml in three patients [5], in non-toxic levels (10–15 ng/ml) in further three patients [1] and a single patient with sirolimus trough levels between 6 and 10 ng/ml [14]. In our study, only six of 11 patients had a trough concentration above 15 ng/ml and two patients below 10 ng/ml, suggesting that low sirolimus trough levels do not exclude this diagnosis. However, our observations show that none of the 35 patients with low-dose sirolimus 2 mg/day developed pneumonitis suggest that low sirolimus trough levels may reduce the frequency of pneumonitis in renal transplant recipients.

In our study, all patients with pneumonitis had severely impaired renal function. Moreover, univariate analyses showed that serum creatinine and GFR are predictive factors for pneumonitis in our cohort. Furthermore, only serum creatinine and GFR are independent predictors for pneumonitis in multivariate analyses. Unfortunately, in several reports, the creatinine levels of the patients suffering pneumonitis are not given [2,3,6,9,10]. However, the three patients reported by Pham *et al.* [1] had elevated creatinine levels (1.9 mg/dl, 4.0 mg/dl and 2.9 mg/dl, respectively) as well. In another series of three cases, creatinine level was given in one patient (160 µmol/l) and a second patient was switched to sirolimus due to a progressive rise of plasma creatinine [5]. A moderately impaired renal function was also present in four patients in a recent report [8]. It is very likely that patients in other reports also had impaired renal function, since the main reason to switch to sirolimus may be advanced calcineurin inhibitor renal toxicity. The tolerance against sirolimus may be altered in the presence of severe renal insufficiency as it is well known for other drug toxicities e.g. neurotoxicity of calcineurin inhibitors in the presence of liver failure [15].

Our data do not support further risk factors for pneumonitis, such as age, gender, underlying disease or concomitant immunosuppressive agents. Univariate analysis showed a lower risk of pneumonitis in patients using tacrolimus, however, the result of the multivariate analysis suggests that this effect is rather a consequence of the lower frequency of pneumonitis in patients with *de novo* use of sirolimus than a hint for a protective value of tacrolimus. Thus, review of the literature showed that 10% of the patients suffering pneumonitis also used tacrolimus.

Treatment of choice of suspected sirolimus-induced pneumonitis is withdrawal of sirolimus. However, some authors also suggested dose reduction of sirolimus as treatment option. In our case series, sirolimus was discontinued in five patients and the sirolimus dose was reduced in the remaining six patients. One of the patients with continued sirolimus treatment had recurrent pneumonitis, however, both episodes were associated with a high sirolimus blood concentration. Recently, recurrence of pneumonitis

during continued but reduced sirolimus dose was also reported by Champion *et al.* [3]. Here, we report the second case with recurrence of pneumonitis after continued low-dose sirolimus exposure, thus sirolimus blood concentrations should be monitored closely and patients should be informed about the possibility of recurrence of pneumonitis.

Steroid treatment of pneumonitis was also used in several case reports (Table 3), however, no convincing data are available to support this strategy. The favourable outcome in our patients without high-dose steroids suggests that steroid treatment is not required in this setting. In accordance with our experience, most patients recovered without sequelae also in other case series. Rarely, development of pulmonary fibrosis and death has been reported [5,7], thus, pneumonitis should be recognized and treated early to avoid a fatal outcome.

The precise aetiology of sirolimus-induced pneumonitis is unknown. Elevated eosinophils and mast cells as described by Morelon *et al.* [2] suggest hypersensitivity against sirolimus as cause of pneumonitis. Our observations that dose reduction of sirolimus leads to regression of pneumonitis favours direct drug toxicity at least in some patients.

*Conflict of interest statement.* Independent from this study, Prof. Rump received a research grant from Wyeth Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

## References

1. Pham PT, Pham PC, Danovitch GM *et al.* Sirolimus-associated pulmonary toxicity. *Transplantation* 2004; 77: 1215–1220
2. Morelon E, Stern M, Israel-Biet D *et al.* Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 2001; 72: 787–790
3. Champion L, Stern M, Israel-Biet D *et al.* Brief communication: sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. *Ann Intern Med* 2006; 144: 505–509
4. Fairbanks KD, Eustace JA, Fine D, Thuluvath PJ. Renal function improves in liver transplant recipients when switched from a calcineurin inhibitor to sirolimus. *Liver Transpl* 2003; 9: 1079–1085
5. Haydar AA, Denton M, West A, Rees J, Goldsmith DJ. Sirolimus-induced pneumonitis: three cases and a review of the literature. *Am J Transplant* 2004; 4: 137–139
6. Dominguez J, Mahalati K, Kiberd B, McAlister VC, MacDonald AS. Conversion to rapamycin immunosuppression in renal transplant recipients: report of an initial experience. *Transplantation* 2000; 70: 1244–1247
7. Lindenfeld JA, Simon SF, Zamora MR *et al.* BOOP is common in cardiac transplant recipients switched from a calcineurin inhibitor to sirolimus. *Am J Transplant* 2005; 5: 1392–1396
8. Morath C, Schwenger V, Ksoll-Rudek D *et al.* Four cases of sirolimus-associated interstitial pneumonitis: identification of risk factors. *Transplant Proc* 2007; 39: 99–102
9. Delgado JF, Torres J, Jose Ruiz-Cano M *et al.* Sirolimus-associated interstitial pneumonitis in 3 heart transplant recipients. *J Heart Lung Transplant* 2006; 25: 1171–1174
10. Chhajed PN, Dickenmann M, Bubendorf L, Mayr M, Steiger J, Tamm M. Patterns of pulmonary complications associated with sirolimus. *Respiration* 2006; 73: 367–374

11. Ursi D, Ieven M, Noordhoek GT, Ritzler M, Zandleven H, Altwegg M. An interlaboratory comparison for the detection of *Mycoplasma pneumoniae* in respiratory samples by the polymerase chain reaction. *J Microbiol Methods* 2003; 53: 289–294
12. Singer SJ, Tiernan R, Sullivan EJ. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; 343: 1815–1816
13. McWilliams TJ, Levvey BJ, Russell PA, Milne DG, Snell GI. Interstitial pneumonitis associated with sirolimus: a dilemma for lung transplantation. *J Heart Lung Transplant* 2003; 22: 210–213
14. Digon BJ, 3rd, Rother KI, Hirshberg B, Harlan DM. Sirolimus-induced interstitial pneumonitis in an islet transplant recipient. *Diabetes Care* 2003; 26: 3191
15. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; 13: 313–326

*Received for publication: 10.12.06*

*Accepted in revised form: 4.6.07*