

Brief Communication: Sirolimus-Associated Pneumonitis: 24 Cases in Renal Transplant Recipients

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Background: Interstitial pneumonitis is an ill-defined side effect of sirolimus, a new immunosuppressant drug recently introduced for patients having organ transplantation.

Objective: To evaluate clinical and laboratory features of sirolimus-associated pneumonitis.

Design: Case series.

Setting: 1 transplantation center in Paris, France.

Patients: 24 patients who had renal transplantation and developed sirolimus-associated pneumonitis, including 8 patients previously reported.

Measurements: Symptoms; laboratory tests, including bronchoalveolar fluid analysis; and computed tomography (CT) of the chest.

Intervention: Withdrawal or dose reduction of sirolimus.

Results: Clinical symptoms included cough (23 patients), fatigue (20 patients), fever (16 patients), and dyspnea (8 patients). Com-

puted tomography of the chest showed reticular and ground-glass opacities (4 patients), bronchiolitis obliterans–organizing pneumonia (19 patients), and lobar consolidation (1 patient). Bronchoalveolar lavage showed lymphocytic (19 patients) or eosinophilic (3 patients) alveolitis or pulmonary hemorrhage (2 patients). A reduction in the sirolimus dose resulted in transient clinical improvement in 2 patients, but discontinuation of drug therapy was eventually necessary in all patients. All patients recovered completely within 6 months.

Limitations: The sirolimus trough level in patients from this single center was higher than that usually used in patients having renal transplantation.

Conclusion: Lymphocytic alveolitis and radiologic bronchiolitis obliterans–organizing pneumonia are the key findings in sirolimus-associated pneumonitis. Sirolimus withdrawal was associated with recovery within 6 months.

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Sirolimus (rapamycin), a macrocyclic lactone isolated from *Streptomyces hydroscopicus*, is a potent immunosuppressive drug that has been successfully used with or without cyclosporine as an alternative to calcineurin inhibitors in patients having organ transplantation (1, 2). Sirolimus inhibits the mammalian target of rapamycin, a protein kinase involved in the proliferation of various cells, including lymphocytes and smooth-muscle cells, in response to cytokines and growth factors. Sirolimus inhibits not only T- and B-cell activation but also growth factor–induced smooth-muscle cell proliferation and migration, a key event in the process of chronic rejection (3).

The main side effects of sirolimus therapy are thrombocytopenia, hyperlipidemia, edema, and rash (1, 4, 5). Sirolimus-associated pneumonitis has also been described after renal, liver, heart, and heart–lung transplantation (6–13). Despite previous case reports (6), sirolimus-associated pneumonitis remains ill-defined because of the absence of specific diagnostic criteria. We report the clinical and pathologic features of 24 cases of pneumonitis in renal transplant recipients who received sirolimus.

METHODS

Between 1996 and 2003, 217 patients having renal transplantation received sirolimus therapy at the Necker Hospital in Paris, France. A total of 128 patients were switched from calcineurin inhibitors to sirolimus to avoid calcineurin inhibitor nephrotoxicity due to chronic allo-

graft nephropathy or to treat post-transplant malignant disease, and 89 patients received sirolimus initially after transplantation. In all patients, sirolimus was used as base immunosuppressive therapy, with a targeted trough level between 12 and 20 ng/mL.

Twenty-four patients (10 men and 14 women) developed pneumonitis that fulfilled the following criteria for presumed sirolimus-associated pneumonitis: exposure to sirolimus before onset of pulmonary symptoms, exclusion of infection or alternative pulmonary disease, bronchiolitis obliterans–organizing pneumonia on computed tomography (CT) of the chest and lymphocytic infiltrates on bronchoalveolar lavage (BAL), new or evolving infiltrates on chest radiography, and clinical improvement after drug withdrawal. We previously reported on 8 of these 24 patients elsewhere (8). The patients' characteristics, immunosuppressive regimens, and sirolimus indications are shown in Table 1.

Bronchoalveolar lavage was done during fiber-optic

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Context

Sirolimus inhibits many of the steps in chronic rejection of transplanted organs. One of its adverse effects, pneumonitis, is still ill-defined.

Content

Of 217 renal transplant recipients who received sirolimus at 1 hospital over 7 years, 24 (11.0%) developed pneumonitis. The presenting features were cough in 23 patients, fatigue in 20 patients, fever in 16 patients, and dyspnea in 8 patients. Ten patients had hypoxemia, and all patients had pulmonary infiltrates. In 19 patients, the infiltrates resembled bronchiolitis obliterans–organizing pneumonia. Bronchoalveolar lavage showed lymphocytic alveolitis in 19 patients. All patients required permanent withdrawal of sirolimus but eventually recovered.

Cautions

There was no control group.

Implications

Pneumonitis is a common, reversible adverse effect of sirolimus therapy.

—The Editors

bronchoscopy at least once in all patients. Total and differential cell counts; specific stainings of BAL fluid (May Grunwald–Giemsa, methenamine silver, and Ziehl); rapid antigen tests for respiratory viruses; and cultures for virologic, bacterial, and mycobacterial evaluation were done after BAL in all patients. To rule out infection, BAL was repeated on 1 to 3 occasions in 12 patients who had a predominance of neutrophils on initial BAL. Twelve patients had 1 BAL procedure, 7 patients had 2, 4 patients had 3, and 1 patient had 4 (Table 2).

No funding was received for this study.

RESULTS**Demographic Characteristics, Sirolimus Dose, Symptoms, and Signs**

Twenty-four of 217 patients (11.0% [95% CI, 7.2% to 16.0%]) who received sirolimus developed pneumonitis (Table 1). Blood trough levels of sirolimus before pneumonitis ranged from 12 to 30 ng/mL (median, 20 ng/mL). Patients had received sirolimus for a median of 5.5 months before respiratory symptoms emerged. Seven patients had progression of pulmonary symptoms over 4 to 6 weeks, and 16 had progression over 2 to 4 days. One patient remained clinically asymptomatic, and pneumonitis was revealed on routine chest radiography. The most common presenting symptoms were cough (23 patients), fatigue (20 patients), fever (16 patients), and dyspnea (8 patients). Two patients had minor hemoptysis. Physical examination showed crackles and crepitus in 10 patients.

Laboratory and Imaging Tests

C-reactive protein levels, measured in all patients, ranged from 6 to 344 mg/L (median, 36 mg/L). The complement level was normal in all 24 patients. Room air arterial blood gas analysis showed moderate hypoxemia (mean PaO₂, 75 mm Hg) in 8 patients; 2 patients had PaO₂ levels less than 60 mm Hg. The remaining 14 patients had normal saturation on room air (oxygen saturation >97%). The results of polymerase chain reaction (PCR) for cytomegalovirus; tests for *Aspergillus* antigen; and serologic tests for *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Aspergillus* were negative. Analysis of BAL cells showed hypercellularity (0.294×10^9 cells/L [SD, 0.666]) with an elevated percentage of lymphocytes (47% [SD, 38%]) in 19 patients and mild eosinophilia ($\geq 5\%$ eosinophils) in 4 patients (Table 2). Eosinophilic alveolitis ($\geq 13\%$ cell count) without blood eosinophilia was seen in 3 patients, and intrapulmonary hemorrhage was seen in 2 patients. In 13 patients, marked lymphocytic alveolitis was present at the first BAL. In 6 additional patients, the first or second BAL showed a neutrophilic pattern that evolved to lymphocytic alveolitis over 2 months. Bronchoalveolar lavage microbiological evaluation remained negative for bacteria (including *Legionella*, *Nocardia*, and acid-fast bacilli), fungi, parasites (*Pneumocystis jirovecii*), and viruses (cytomegalovirus; herpesviruses 1 and 2; and respiratory syncytial, influenza, and parainfluenza viruses 1, 2, and 3) in all 12 patients who had repeated BAL. Neither antineutrophil cytoplasm nor antiglomerular basement membrane antibodies were seen in the 2 patients with the BAL findings of hemorrhage.

All patients had pulmonary infiltrates on radiography. Computed tomography of the chest showed patchy bilateral asymmetrical peripheral consolidations (bronchiolitis obliterans–organizing pneumonia-like aspect) in 19 patients, reticular and ground-glass opacities in 4 patients, and lobar consolidation in 1 patient. These opacities predominantly involved the lower lobe in 15 patients and were diffuse in 9 patients. Computed tomography did not reveal any pleural or mediastinal abnormalities.

Management and Outcome

Sirolimus therapy was discontinued immediately in 9 patients. In 13 patients, sirolimus therapy was discontinued after 4 to 12 days of ofloxacin and ceftriaxone therapy yielded no improvement. No patients required admission to the intensive care unit. Nineteen of 24 patients improved spontaneously within 2 weeks of sirolimus withdrawal, and 3 of 24 received corticosteroids (1 mg/kg of body weight per day) for 2 weeks because pulmonary and general symptoms persisted after sirolimus withdrawal. Results of chest radiography and CT returned to normal within 6 months in 22 patients. The sirolimus dose was initially reduced in 2 patients with clinical remission. However, clinical relapse in 1 patient and persistence of opacities on CT in the other patient led to sirolimus with-

Table 1. Characteristics of Renal Transplantation Recipients with Sirolimus-Associated Pneumonitis*

Patient Number	Age at Pneumonitis Diagnosis, y	Sex	Underlying Disease	Indication for Sirolimus Therapy	Time since Transplantation before Switch to Sirolimus, mo	Other Immunosuppressive Therapy	Duration of Sirolimus Therapy, mo
1	55	M	IgA nephropathy	De novo use	NA	Cyclosporine, prednisolone	11
2	49	M	Hypertensive nephropathy	De novo use	NA	Mycophenolate mofetil, prednisolone	1
3	57	F	FSGS	De novo use	NA	Mycophenolate mofetil, prednisolone	18
4	51	F	Polycystic kidney	De novo use	NA	Mycophenolate mofetil, prednisolone	51
5	69	M	IgA nephropathy	Skin cancer	112	Prednisolone	1
6	63	M	Uropathy	Skin cancer	193	Prednisolone	1
7	56	M	IgA nephropathy	Skin cancer	293	Azathioprine, prednisolone	1
8	57	F	IgA nephropathy	Skin cancer	116	Prednisolone	1
9	52	F	Not determined	Skin cancer	81	Azathioprine, prednisolone	2
10	67	M	IgA nephropathy	Lymphoma	106	Prednisolone	2
11	67	M	Diabetes	Chronic allograft neuropathy	23	Mycophenolate mofetil, prednisolone	18
12	63	M	Polycystic kidney	Chronic allograft neuropathy	47	Prednisolone	12
13	55	M	Diabetes	Chronic allograft neuropathy	121	Prednisolone	2
14	53	M	Polycystic kidney	Chronic allograft neuropathy	4	Azathioprine, prednisolone	8
15	66	F	Not determined	Chronic allograft neuropathy	99	Prednisolone	3
16	65	F	Crescentic glomerulonephritis	Chronic allograft neuropathy	116	Prednisolone	1
17	63	F	Polycystic kidney	Chronic allograft neuropathy	6	Mycophenolate mofetil, prednisolone	11
18	58	F	IgA nephropathy	Chronic allograft neuropathy	177	Mycophenolate mofetil, prednisolone	11
19	53	F	Diabetes	Chronic allograft neuropathy	23	Mycophenolate mofetil, prednisolone	2
20	50	F	Tubulointerstitial nephropathy	Chronic allograft neuropathy	133	Prednisolone	3
21	50	F	Alport syndrome	Chronic allograft neuropathy	136	Azathioprine, prednisolone	9
22	49	F	IgA nephropathy	Chronic allograft neuropathy	101	Azathioprine, prednisolone	22
23	42	F	IgA nephropathy	Chronic allograft neuropathy	3	Azathioprine, prednisolone	12
24	39	F	Uropathy	Chronic allograft neuropathy	64	Prednisolone	9

* The median age of the patients was 55.5 years, and the median duration of sirolimus therapy was 5.5 months. Data for patients 1, 2, 3, 12, 13, 16, 19, and 22 have been reported previously (8). F = female; FSGS = focal and segmental glomerulosclerosis; M = male; NA = not applicable.

drawal. No alternative pulmonary disease was identified in the 24 patients. As of September 2005, all 24 patients have remained free of pneumonitis recurrence for 1 to 6 years.

Of the 600 transplant recipients who did not receive sirolimus during the same period, none developed similar pneumonitis, that is, pneumonitis characterized by bronchiolitis obliterans–organizing pneumonia on chest CT or BAL with predominant lymphocytes.

DISCUSSION

Lung toxicity associated with sirolimus therapy in organ transplant recipients has been reported in only 80 published cases (13). To our knowledge, the present report of

24 cases is the largest published series of sirolimus-associated pneumonitis after renal transplantation and provides new information about this disease. The present and previously reported cases (6) show that sirolimus-associated pneumonitis can mimic infection and that its severity is usually mild to moderate when sirolimus therapy is discontinued. In our series, 10 of 24 patients had hypoxemia but none required mechanical ventilation. However, previous reports include 1 renal transplant recipient who required mechanical ventilation (6) and 2 deaths in patients who received heart transplants (13, 14). Because of the nonspecific clinical symptoms, CT and BAL can help identify sirolimus-associated pneumonitis. In 19 of 24 of our pa-

Table 2. Cell Content of Bronchoalveolar Lavage Samples at Diagnosis of Sirolimus-Associated Pneumonitis in Renal Transplant Recipients*

Patient Number	Total Cells, $\times 10^9$ cells/L	Macrophages, %	Lymphocytes, %	Polymorphonuclear Leukocytes, %	Eosinophilic Leukocytes, %	BAL Procedures Performed, n
1	0.195	13	85	2	0	1
2	0.280	93	0	7	0	2
3	0.150	72	18	10	0	2
4	0.250	11	58	26	3	2
5	0.540	58	41	1	0	3
6	0.350	34	46	19	1	3
7	0.015	45	33	8	14	1
8	0.130	20	75	5	0	1
9	0.960	27	61	10	2	1
10	0.080	78	20	2	0	1
11	0.270	74	21	5	0	2
12	0.436	28	66	4	2	4
13	0.390	80	16	4	0	2
14	0.400	21	68	8	3	1
15	0.210	65	33	1	1	2
16	0.310	58	48	2	2	1
17	0.160	65	25	10	0	1
18	0.250	43	31	12	14	1
19	0.440	59	36	5	0	2
20	0.350	0	58	0	0	3
21	0.200	76	9	2	13	1
22	0.390	17	75	7	1	1
23	0.00	64	9	30	0	2
24	0.260	0	41	4	5	1

* Hemosiderin laden was positive for patients 2 and 23. BAL = bronchoalveolar lavage.

tients, CT showed a bronchiolitis obliterans–organizing pneumonia pattern in accordance with that reported in renal, cardiac, and lung transplant recipients (6, 7, 11, 13), a finding that is more consistent with drug-induced pneumonitis than with infection.

At diagnosis, BAL showed hypercellularity with lymphocytosis (>20% lymphocytes). Of interest, 11 of 24 patients initially had a misleading predominance of neutrophils in the first BAL, as previously described in drug-induced hypersensitivity (15). The absence of any microorganisms despite repeated BAL and the failure of empirical antibiotic treatment ruled out infection in these patients. Bronchoalveolar lavage seems to be helpful in diagnosing sirolimus-associated pneumonitis; 22 of 24 of our patients had BAL evidence of lymphocytic or eosinophilic alveolitis, which confirms the results of previous studies (6, 8). Alveolar hemorrhage was much less frequent (2 of 24 patients).

All of our patients recovered without sequelae after sirolimus was withdrawn. However, 1 case of pulmonary fibrosis diagnosed 10 months after sirolimus withdrawal has been reported (12). Despite initial improvement in our case series, decreasing the dose was inadequate and all patients required discontinuation of sirolimus therapy. The long-term association of sirolimus and pulmonary fibrosis is unknown.

Although we cannot draw any firm conclusions, our series suggests that the incidence of sirolimus-associated pneumonitis might be higher in patients who switched

from calcineurin inhibitors to sirolimus (20 of 128 patients, or 15.6% [CI, 9.8% to 23.1%]) than in those who started sirolimus therapy initially after transplantation (4 of 89 patients, or 4.5% [CI, 1.2% to 11.1%]). This observation is similar to recent observations in cardiac transplant recipients who switched from a calcineurin inhibitor to sirolimus (13). The incidence of other side effects of sirolimus therapy, such as proteinuria, anemia, and mouth ulcers, also seems to increase when this drug is used to replace calcineurin inhibitors (16). Furthermore, the duration between the introduction of sirolimus and the onset of pneumonitis might be shorter in patients who switched to sirolimus than in those who initially received it (median duration, 3 vs. 14 months, respectively), which suggests either variation in susceptibility or different mechanisms. Other factors that might be related to the risk for sirolimus-associated pneumonitis include age, underlying disease, concomitant immunosuppressive therapy, and serum levels of sirolimus.

Previous reports suggest that sirolimus-induced lung toxicity might be dose-dependent (7). Although 2 patients in our series and in another previously published series (7) improved after the dose of sirolimus was decreased, both of our patients eventually required discontinuation of sirolimus therapy. Previous reports included patients with low sirolimus trough levels (6, 13). Finally, presence of lymphocytes and eosinophils on BAL suggests an immune reaction mediated by T lymphocytes, predominantly CD4 cells.

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