

Sirolimus-Associated Interstitial Pneumonitis in a Liver Transplant Patient

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Sirolimus (Rapamune, Wyeth) is a potent immunosuppressive agent that inhibits T-lymphocyte proliferation induced by cytokine stimulation; since its introduction in 1999 for use in renal transplant patients it has also been used by an increasing number of liver transplant centers.¹ Pulmonary toxicity has been recognized as a potential serious complication with sirolimus therapy; over 40 reports have associated it with interstitial pneumonitis. However, most of these reports have involved renal transplant patients,² and we are aware of only 2 previous reports of interstitial pneumonitis in liver transplant patients taking sirolimus.^{3,4} We report a case of sirolimus-induced interstitial pneumonitis in a liver transplant patient.

Case Report

A 28-year-old woman presented to the emergency department with a 3-day history of cough, shortness of breath, and weakness. She had no prior history of pulmonary disease. Four years prior to presentation she received a liver transplant secondary to fulminant hepatic failure of unknown cause. Her initial immunosuppressive regimen consisted of tacrolimus (Prograf, Fujisawa Healthcare) and prednisone. Eleven months prior to presentation, allograft dysfunction was noted and acute rejection was diagnosed by liver biopsy. She received medroxyprogesterone (Solu-Medrol, Pfizer) bolus therapy, and mycophenolate mofetil (CellCept, Roche) 1 g twice daily was added to the immunosuppressive regimen. Six weeks prior to presentation she was hospitalized for persistent allograft dysfunction and renal insufficiency. A liver biopsy demonstrated bridging fibrosis and resolving rejection. Due to the presence of renal insufficiency, tacrolimus was discontinued and sirolimus 5 mg/day was started in addition to prednisone 10 mg/day and mycophenolate mofetil 1 g twice daily.

Additional medications included ursodeoxycholic acid, insulin glargine (Lantus, Aventis), and metoclopramide.

On presentation she reported subjective fever, cough, shortness of breath, occasional nausea and vomiting, mild abdominal distention without pain, and lower extremity swelling. She denied headaches, diarrhea, or hemoptysis.

Physical examination revealed a temperature of 101.5°F, heart rate of 122 beats per minute, and blood pressure of 83/55 mm Hg. Breathing was moderately labored, with a respiratory rate of 20 breaths per minute. Oxygen saturation by pulse oximetry was 91% on room air. The patient had a mildly distended abdomen but no tenderness to palpation. Bilateral inspiratory crackles were evident on chest auscultation.

Initial testing revealed a white blood cell count of 23,000/mm³, hematocrit of 28%, and platelet count of 153,000/mm³. International normalized ratio was 1.0, blood urea nitrogen was 27 mg/dL (normal: 7–18 mg/dL), and serum creatinine was 2.0 mg/dL (normal: 0.6–1.3 mg/dL). Additional laboratory values were as follows: total protein, 4.5 g/dL; albumin, 1.7 g/dL; total bilirubin, 6.5 mg/dL; alkaline phosphatase, 358 U/L (normal: 50–136 U/L); aspartate aminotransferase, 103 U/L (normal: 15–37 U/L); and alanine aminotransferase, 127 U/L (normal: 30–65 U/L). An abdominal ultrasound revealed ascites; however, paracentesis found no evidence of peritonitis. Chest x-ray showed bilateral infiltrates involving the left upper lobe, right middle lobe, and bibasilar areas. Arterial blood gas analysis showed a PO₂ of 59 and oxygen saturation of 88% on room air. Sirolimus level at admission was elevated at 26 ng/mL (normal: 12–20 ng/mL).

During the subsequent hours the patient was placed on neosynephrine for blood pressure support, and sirolimus was stopped. The hypoxemia responded to supplemental oxygen. She was given Solu-Medrol at a dose of 500 mg intravenously and, after appropriate cultures, placed on broad-spectrum antibiotic coverage, including vancomycin, piperacillin/tazobactam (Zosyn, Wyeth),

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and levofloxacin, and fluconazole (Diflucan, Pfizer). Mycophenolate mofetil was continued.

After the initial 24 hours, the patient's clinical course gradually improved. Multiple blood and sputum cultures were negative. She had a bronchoscopy with bronchoalveolar lavage (BAL) on her third day in the hospital, and appropriate stains and cultures of BAL fluid showed no evidence of bacterial, fungal, mycobacterial, or viral organisms.

After 8 days of hospitalization, the patient was feeling better and did not require oxygen. A repeat chest x-ray done 2 weeks later showed resolution of bilateral infiltrates. She was discharged home on tacrolimus, prednisone, and mycophenolate mofetil.

Discussion

Sirolimus is an immunosuppressive agent approved by the US Food and Drug Administration (FDA) in 1999 for use in renal transplant patients. The introduction of sirolimus allowed transplant physicians to develop various strategies to provide adequate immunosuppression while minimizing the nephrotoxic effects associated with calcineurin inhibitor therapy.¹ Although the most common adverse effects of sirolimus therapy include hyperlipidemia and myelosuppression, there are numerous reports of pulmonary toxicity associated with sirolimus therapy. Most of the cases reported have involved renal transplant patients, although cases have been reported after lung⁵ and heart⁶ transplants as well. As of 2001, the FDA had recognized 34 cases of interstitial pneumonitis associated with sirolimus therapy. Thirty-two of those cases were in renal transplant patients, while only 1 was associated with a liver transplant. By 2004, an additional 9 cases had been reported in the literature.⁷ To the best of our knowledge, only 1 pediatric and 1 adult case have been reported of sirolimus-associated interstitial pneumonitis in liver transplant patients.^{3,4} Indeed, a recent retrospective analysis of sirolimus-related complications in liver transplant patients⁸ did not mention interstitial lung disease as a complication, although pleural effusions, which resolved after sirolimus therapy was discontinued, were noted in 16% of patients.

Implicating a particular cause of pulmonary injury in immunocompromised patients can be difficult.⁹ The diagnosis of drug-induced lung disease usually is based on several criteria: 1) a history of drug exposure, 2) clinical, imaging, and histopathologic patterns that are consistent with earlier observations with the same drug, 3) exclusion of other lung disease, 4) improvement following discontinuation of the suspected drug, and 5) recurrence of symptoms on rechallenge (although, for ethical reasons, this is usually not done).¹⁰ Clinically, the diagnosis of

drug toxicity rests on the following: a temporal relationship between use of a particular agent and the subsequent development of symptoms, and improvement of pulmonary function after withdrawal of the agent.⁹

Our patient developed clinical and radiologic evidence of pneumonitis within 6 weeks of exposure to sirolimus. She had no prior history of pulmonary disease, extensive testing failed to reveal an infectious cause, and the interstitial pneumonitis promptly resolved after discontinuation of sirolimus despite continuing all other medications. Bilateral lower extremity edema, which has been reported in 57% of liver transplant patients on sirolimus⁸ was also present in our patient. Although a total white blood cell count and differential was not performed on the fluid obtained from BAL, no diagnostic findings are found on BAL fluid in patients with drug-induced disease.¹⁰

Of the cases reported to the FDA, 50% developed sirolimus-associated pneumonitis within the first 6 months of initiation of therapy. Symptoms were variable but included dyspnea, cough, fever, and malaise, all of which were present in our patient. Lung biopsy can reveal a spectrum of disease including organizing pneumonia, bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis, focal fibrosis, or the presence of alveolar hemorrhage.^{5,7,11} Although high-dose steroids were used in our patient and may have contributed to her improvement, the role of high-dose steroids in sirolimus-induced lung injury remains unknown. Also, the exact pathogenic mechanism of sirolimus-induced pulmonary toxicity is not known. However, a dose-related effect has been suggested, with clinical improvement noted in some patients after sirolimus dose reduction.⁷ Our patient did have a high sirolimus serum level on initial presentation, which could have contributed to the pulmonary toxicity.

In conclusion, interstitial pneumonitis is a serious potential consequence of sirolimus therapy in liver transplant patients. The development of cough or dyspnea in patients taking sirolimus should trigger a prompt evaluation and consideration for a change in the immunosuppressive regimen. As the use of sirolimus in liver transplantation increases, clinicians should remain alert to the possibility of drug-induced pulmonary toxicity.

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Review

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Since first described by Sehgal in 1995, sirolimus has gained access into many transplant arenas as a potent immunosuppressant.¹ In fact, the immune suppression effects of sirolimus are presently well recognized in the treatment of chronic rejection, calcineurin inhibitor-associated renal or neural toxicity, and steroid-resistant allograft rejection, as well as for preemptive immunosuppression.²⁻⁴ The popularity of sirolimus in the liver transplantation community has continued to increase over the last 5 years, primarily as an alternative to calcineurin inhibitors.

Sirolimus' mechanism of action is apparently unrelated to calcineurin receptor sites, but it is able to inhibit interleukin-2-mediated pathways.⁵ Sirolimus is thought to be devoid of immune suppression-related neurotoxicity, diabetogenesis, and nephrotoxicity.⁶ The use of sirolimus in liver transplant recipients is off-label and it is approved by the FDA only in kidney transplantation for calcineurin inhibitor-related nephrotoxicity.⁷

Preliminary results for sirolimus in liver transplant recipients were quite favorable. Over time, however, reports of sirolimus-related complications began to

appear, including leukopenia, thrombocytopenia, hypertriglyceridemia, hypercholesterolemia, mouth ulceration, wound infection and dehiscence, edema, joint pain, and pulmonary changes.⁸⁻¹² We have reported sirolimus-related adverse effects from the largest group of patients receiving sirolimus to date.¹³

In their case report, Barnett and Herrera discuss another type of sirolimus complication, interstitial pneumonitis. Sirolimus-related interstitial pneumonitis has been reported in kidney, lung, islet cell, and heart transplant recipients; although widely described in kidney and lung transplant recipients, reports in liver transplant patients have thus far been rare.¹⁴⁻²⁸ The FDA continues to monitor reports of sirolimus-related lung injury, as mentioned by the authors. Two groups, Morelon et al and Singer et al, discuss a large number of transplant recipients suffering from interstitial pneumonitis within 6 months of starting sirolimus therapy, resolving, in several of the patients, once the drug was discontinued.^{24,25} One troubling aspect of sirolimus-related lung disease is its various presentations, ranging from interstitial pneumonitis and bronchiolitis obliterans with organizing pneumonia to alveolar hemorrhage.

Our group has reported more than 25 cases of sirolimus-related cardiac or pulmonary complications among liver transplant recipients.²⁹ Twenty patients developed lung injury, mostly pleural effusion, and 5 had pericardial effusion. None of these complications were gender-specific, morbidity-related, or serum level-responsive. The pleural effusions were diagnosed using chest x-ray, computerized tomography, and echocardiogram. We did not perform invasive tests such as needle aspirate of the fluid or BAL on many of the patients. None of the patients had fever or chills, but rather complained of fatigue and persistent cough. Their work-ups were negative for cardiac disease or infection and sirolimus had been started within weeks of the diagnosed lung injuries. In all cases, complete resolution of the effusions occurred over a 4-6 month period once sirolimus was discontinued.

The case that caused the most concern involved a 60-year-old man who was more than 1 year removed from liver transplantation. He experienced progressive dyspnea over a 6-month period that resulted in an inability to ambulate. His symptoms started 4 months after conversion from tacrolimus to sirolimus for renal insufficiency. He was admitted to the hospital with hypoxia. The work-up revealed markedly high right heart pressures. The working diagnosis was pulmonary hypertension. Sirolimus was discontinued and epoprostenol was given. The patient's physical symptoms started to regress after 6 months, while echocardiogram showed slow improvement in the right-sided pressures. Twelve months removed from sirolimus, right heart pressures had returned to normal,

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epoprostenol was discontinued, and the patient returned to his previous life style.

The exact pathophysiological mechanism of sirolimus in lung-related injuries, as well as other sirolimus-related injuries, is unknown.¹⁴ There is speculation that a capillary leak-type syndrome may be involved.^{3,30} Our experience shows that diuretic therapy is not beneficial and is in fact contraindicated, as many of these patients are suffering from calcineurin-related renal insufficiency.

We agree with the authors' conclusion that upper respiratory tract symptoms in any transplant patient receiving sirolimus need extensive investigation and careful surveillance. In the meantime, sirolimus will continue to be tested for durability in the posttransplant community, at least until calcineurin-type agents that spare the kidneys are developed.

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