Fever, Erythroderma, Abdominal Pain, and Renal Failure Following Initiation of Indinavir Therapy

Indinavir (Crixivan, Merck Pharmaceuticals, West Point, PA), a recently released HIV protease inhibitor, is a popular component of combination antiretroviral therapy; treatment with such combinations results in a marked decrease in viral load and an increase in CD4 cells in HIV-infected persons [1]. The side effects are not prohibitive and most commonly include gastrointestinal intolerance, an elevated indirect bilirubin level, and nephrolithiasis. The latter is preventable with adequate fluid intake [2]. I describe a case of life-threatening toxicity related to the use of indinavir.

A 32-year-old HIV-infected, diabetic male was admitted to the hospital with fever, rash, and abdominal pain. Two weeks before admission, indinavir was added to a regimen of zidovudine, lamivudine, dapsone, and insulin. His serum creatinine level was 1.0 mg/dL; he had baseline proteinuria (excretion rate, 1 g/24 h), and his CD4 cell count was 104/mm³.

Seven days before admission, the patient developed malaise and fever. Five days before admission, he received cefaclor for increasing fever with no localizing symptoms. On the following day, facial swelling developed. Treatment with cefaclor was discontinued, and methylprednisolone was administered. Over the next 3 days, generalized erythema, high fever, severe weakness, and abdominal pain developed. Treatment with indinavir was discontinued the night before admission. Physical examination on admission revealed a temperature of 39.9°C, tachycardia, and a blood pressure of 135/85 mm Hg. Generalized erythroderma was present. The oropharynx was diffusely erythematous. The abdomen was distended and diffusely tender, with pronounced rebound tenderness. Bowel sounds were normal.

Laboratory tests revealed the following values: leukocytes, 5.6/mm³ (neutrophils, 67%; immature forms, 15%; lymphocytes, 12%; and eosinophils, 6%); creatinine, 7.5 mg/dL; and blood urea nitrogen (BUN), 72 mg/dL. Urinalysis revealed 5–10 RBCs and 10–20 WBCs per high power field. A CT scan of the abdomen and pelvis revealed diffuse mesenteric edema, diffuse edema of the retroperi toneal fat, bilaterally enlarged kidneys, and two nonobstructing right renal calculi.

On admission, all medications except insulin were withheld, and treatment with intravenous hydration, cefazolin, and gentamicin was given. After 48 hours, his abdominal pain and distension had abated, the erythroderma had nearly resolved, and the fever had decreased markedly, but the patient remained oliguric. Blood and urine cultures were negative. Other laboratory values were: absolute eosinophil count, 900/mm³; BUN, 98 mg/dL; and creatinine, 11.3 mg/dL. Antibiotic therapy was discontinued, and hemodialysis was initiated. A renal biopsy was performed, and treatment with prednisone (1 mg/kg·d) was started.

By the ninth hospital day the patient was eating well, his skin was exfoliating superficially, and he was excreting urine. Examination of the renal biopsy specimens showed acute tubular necrosis superimposed on early focal segmental glomerular sclerosis. Hemodialysis and treatment with prednisone were discontinued. After 4 weeks, his creatinine level had stabilized at 2.4 mg/dL, and he was excreting 22 g of protein/24 h. The patient declined rechallenge with indinavir but tolerated resumption of treatment with dapsone, zidovudine, and lamivudine.

Indinavir is implicated as the cause of this patient’s syndrome because of the onset of symptoms shortly after the initiation of therapy, the rapid improvement in his condition after the medication was withdrawn, the successful rechallenge with his other medications, and the lack of any identified infectious etiology. It is possible that cefaclor caused the rash, but the initial symptoms of malaise and fever preceded the initiation of cefaclor therapy. I believe the peritonitis represented inflammation of serosal surfaces, analogous to his erythroderma.

The pathophysiology of the patient’s renal failure is not clear. There was no documented hypotension, and the renal failure progressed despite aggressive hydration. The biopsy results suggested underlying HIV nephropathy, but acute tubular necrosis is not described as part of that syndrome [3]. Nephrolithiasis occurs with administration of indinavir but is not usually associated with renal dysfunction, and it generally resolves with hydration [4]. Renal failure with eosinophilia has been reported with administration of ritonavir; the mechanism of this side effect has not been described [5].

Fever occurred in <2% of patients in clinical trials of indinavir; erythroderma and renal failure are not described [4]. It is likely that in clinical trials, treatment with indinavir has been discontinued before symptoms became as severe as those reported herein. In this case, an adverse drug reaction was not considered, and the patient continued treatment with a new medication despite the fever and rash that developed shortly after therapy was initiated.

The protease inhibitors are a critical component of successful therapy for HIV infection. The medical literature and the popular press have reported impressive results as well as strong warnings regarding the possibility that resistance may develop if doses are missed or the drug is discontinued [6, 7]. Because of accelerated approval of protease inhibitors by the U.S. Food and Drug Administration, certain adverse effects may occur infrequently with expanded use of these agents. Clinicians should be alert to the potential for previously undescribed, life-threatening reactions with this new class of agents and should not let concerns about possible resistance outweigh simple clinical judgment.

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References
High-Dose Ampicillin Plus Streptomycin for Treatment of a Patient with Severe Infection Due to Multiresistant Enterococci

Treatment options for patients infected with multiply resistant Enterococcus faecium are limited [1–3]. We describe a patient with intraabdominal and bacteremic infection due to E. faecium that was resistant to vancomycin, ampicillin, and high levels of gentamicin but susceptible to streptomycin. The severity of his infection led us to perform in vitro studies to help predict in vivo response as a guide to managing antibiotic therapy.

A 53-year-old man with chronic renal failure requiring continuous ambulatory peritoneal dialysis developed fevers, chills, constipation, and a cloudy dialysate with 1,030 WBCs/mm² and 95% neutrophils. Cultures of peritoneal fluid yielded E. faecium, and the patient was treated empirically with iv vancomycin and gentamicin. After 3 days of therapy, cultures of one of two blood specimens drawn from separate venipuncture sites yielded E. faecium that was resistant to ampicillin and vancomycin.

Subsequently, cultures of peritoneal fluid yielded a non-spore-forming anaerobic gram-positive rod and a viridans streptococcus. The patient underwent hemicolecotomy because of colitis with perforation. He had persistent enterococcal wound infection postoperatively, and cultures of blood and of a peripheic abcess aspirated under CT scan guidance yielded E. faecium. The MICs/MBCs for both the original and postsurgical enterococcal isolates from blood and peritoneal fluid abscesses were as follows (in µg/mL): vancomycin (>256/>256); ampicillin (32/>1,024); penicillin (128/>128); gentamicin (1,000/>1,000); streptomycin (32/64); ciprofloxacin (256/>256); chloramphenicol (2/>128); doxycycline (0.125/>64); novobiocin (0.5/>64); clinafoxacin (8/32); RP59500 (0.5/>128); teicoplanin (32/not tested); oxazolidinone U-100592 (2/>128); and oxazolidinone U-100766 (2/>128). The patient was treated for 1–3 days with chloramphenicol, doxycycline, and ciprofloxacin. Because of continuing signs of sepsis and the susceptibility of the isolate to the new streptogramin antibiotic RP59500 (quinoxpristin/dalfopristin), therapy with this agent was started. During the next 3 days, the patient developed severe, diffuse arthralgias and his liver enzymes became elevated; therapy with RP59500 was stopped. The patient continued to have fever and leukocytosis (maximum WBC count, 38,900/mm³), and cultures of blood yielded E. faecium with the same susceptibility pattern as the previous blood and peritoneal isolates.

RP59500 therapy was restarted at a lower total daily dose; however, a CT scan and wound drainage cultures revealed that the patient continued to have persistent intraabdominal infection, and thus RP59500 therapy was stopped. Because of a history of an allergy to penicillin, the patient underwent desensitization. He was treated with 2 g of ampicillin every 6 hours iv (a high dose in view of chronic renal failure and hemodialysis) plus streptomycin (500 mg twice a week). His blood cultures became negative. After 6 weeks of treatment, his wound healed, and a CT scan revealed resolution of the abscess. He had no recurrence of infection at a 6-month follow-up visit.

Macrobrotb dilution susceptibility testing and time-kill synergy studies were performed in strict compliance with the guidelines established by the National Committee for Clinical Laboratory Standards [4, 5]. Time-kill studies were performed with use of the following agents (concentration in µg/mL) alone and in combination: ampicillin (32), clinafoxacin (8), streptomycin (20), RP59500 (6), and vancomycin (20). Synergy was defined as a >2 log₁₀ increase in kill with the combination compared with its more active constituent at 24 hours, and indifference was defined as <1 log₁₀ change (increase or decrease) in killing at 24 hours.

The only combination that was synergistic was streptomycin plus ampicillin, with an increased kill of 3.6 log₁₀ at 24 hours (figure 1). The combination of vancomycin with ampicillin and clinafoxacin had a 0.9 log₁₀ increased kill at 24 hours (indifference). All other combinations, including those with RP59500, had no increased kill.

Our patient required treatment for persistent enterococcal infection in a wound, in blood, and in peritoneal abscesses. Although chloramphenicol, doxycycline, and RP59500 exhibited in vitro activity against our patient’s isolate, therapy with these agents proved to be ineffective for our patient or was poorly tolerated. Oxazolidinones, clinafoxacin, and novobiocin had in vitro activity against our patient’s isolate and warrant further study but were not available for our use. The final attempt at treatment included streptomycin and relatively high-dose ampicillin (8 g/d for a patient undergoing hemodialysis). Despite the risks of high-dose ampicillin (e.g., seizures) and streptomycin (e.g., ototoxicity and nephrotoxicity), this combination was chosen based on our in vitro data, based on the results of other investigators [6–9], and because a peak serum ampicillin concentration of >100 µg/mL can be achieved following a dose of 2 g [10]. Because the MICs of teicoplanin and ampicillin for this strain were measurable and because this strain did not demonstrate high-level aminoglycoside resistance to streptomycin, it is different from many multiresistant epidemic strains that may not respond to therapy as favorably as our isolate.

Our patient’s therapy was successful as demonstrated by the improvement in his clinical condition, the normalization of his laboratory...