



Letters

Successful use of rifampin in a patient with Stevens-Johnson syndrome to rifabutin

Stevens-Johnson Syndrome (SJS) is a severe cutaneous adverse reaction that is generally considered an absolute contraindication to future use of the offending agent owing to the high risk of morbidity and mortality. Although large studies or validated assays that predict clinical cross-reactivity are lacking, potentially cross-reactive medications are often avoided. Restricting medication use can, however, also pose health risks when efficacious therapies are limited. This is particularly true for mycobacterial infections, in which rifamycins can be integral to effective treatment¹ but have been associated with a significant risk of SJS.² In this report, we describe the successful use of a novel dose escalation protocol for rifampin in a patient with a history of SJS to rifabutin.

The patient was a 63-year-old man who had previously undergone renal transplant and was admitted to the hospital for disseminated *Mycobacterium avium complex* (MAC) with clavicular osteomyelitis. His medical history was notable for chronic kidney disease stage III, insulin-dependent diabetes mellitus, and seronegative rheumatoid arthritis. His immunosuppressive regimen included mycophenolate sodium, cyclosporine, and prednisone 10 mg daily.

MAC was initially treated with ethambutol 1600 mg once daily and azithromycin 500 mg once daily. Owing to recurrence of high-grade fever after 12 days of therapy, rifabutin 300 mg once daily was added. He was concurrently diagnosed with herpes simplex virus-1 stomatitis and esophagitis, which resolved after a 10 day course of acyclovir. After completing acyclovir, valacyclovir prophylaxis was initiated.

Three weeks into MAC therapy, the patient developed a diffuse morbilliform rash and fever of 38.4°C. Rifabutin, valacyclovir, and ethambutol were discontinued, but he remained on azithromycin. Five days later, he developed a high-grade fever (maximum temperature of 39.5°C) and hypotension. These symptoms were initially attributed to septic shock, although blood cultures only demonstrated delayed growth of MAC. Mycophenolate sodium was discontinued because of severe lymphopenia, but he continued to receive cyclosporine and prednisone to prevent renal graft rejection.

Peripheral blood eosinophil counts remained low (0–140 cells/mm³) with no acute changes, although leukopenia and continuous use of low-dose prednisone may have masked eosinophilia.

Lymphopenia attributed to disseminated MAC and chronic immunosuppression remained stable, and evaluation for human herpes virus 6/7 was negative. No visceral involvement, lymphadenopathy, or other hematologic changes occurred, and his presentation was therefore considered to be less consistent with drug-induced hypersensitivity syndrome (DIHS). The patient developed progressive erythroderma, desquamation involving less than 10% of body surface area, and painful herpes simplex virus–negative vesicles and ulcerations on the oral and urogenital mucosa. There were no reported bullae, and Nikolsky sign was negative. The final diagnosis was SJS to rifabutin, given the typical symptomatology, temporal relationship between introduction of rifabutin and onset of rash, and ability to restart ethambutol and valacyclovir without any adverse reactions. Skin biopsy was not performed. SJS was managed supportively with intravenous fluids, parenteral nutrition, and analgesia. Mucocutaneous lesions healed over the next month.

The patient remained bacteremic after 1 month of azithromycin and ethambutol, prompting the Infectious Disease Service to recommend addition of a rifamycin. There are limited clinical data regarding rifamycin cross-reactivity. Elevated drug-specific immunoglobulin E's to multiple rifamycins (rifampin, rifabutin, rifaximin, and rifapentine) were measured in 1 patient with history suggestive of anaphylaxis to oral rifaximin and topical rifamycin.³ In light of our patient's tenuous clinical status, we developed a dose escalation protocol for rifampin (Table 1) that he successfully tolerated for 2 weeks before his death from disseminated MAC. Rifampin was introduced 6 weeks after rifabutin was discontinued.

Rifamycins are a family of bactericidal drugs, including rifampin, rifabutin, rifapentine, and rifaximin, which inhibit prokaryotic DNA-dependent RNA polymerase. Rifabutin and rifampin share an aliphatic chain that connects 2 ends of a naphthoquinone core, but they have many structural dissimilarities and bind to different polymerase subunits.^{4,5} Efficacy is comparable for the treatment of pulmonary tuberculosis,¹ but rifabutin is often preferred because it is a less potent inducer of cytochrome P450 3A4⁴ with fewer medication interactions.

Tolerance of rifabutin was demonstrated in 6 patients with human immunodeficiency virus and tuberculosis who had challenge-validated DIHS to rifampin. After resolution of DIHS reactions to rifampin challenge, all patients tolerated a complete, unmodified course of rifabutin.⁶ A second case report suggested the potential for cross-reactivity between rifamycins but described early identification of DIHS and consequently reduced morbidity using a dose escalation approach. This patient with MAC septic arthritis developed SJS, hepatitis, renal abnormalities, and peripheral eosinophilia suggestive of comorbid DIHS after treatment with both rifampin and rifabutin. Patch testing was interpreted as

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Table 1
Dose Escalation Protocol for Rifampin, With Doses Given Enterally Once Daily

Day	Rifampin dose (mg)	Percentage of treatment dose
1	6	1
2	12	2
3	24	4
4	48	8
5	96	16
6	192	32
7	300	50
8 + n	600	100

positive to rifabutin and as an irritant reaction to rifampin, so rifampin was introduced at one-quarter of the therapeutic dose. After 3 days of this dose, she developed transaminitis and C-reactive protein elevation attributed to DIHS that resolved shortly after discontinuing therapy.⁷

Because these limited data suggested the potential for incomplete clinical cross-reactivity between rifamycins, we elected to give rifampin in a manner analogous to delayed-type hypersensitivity desensitization protocols. Traditionally, these have been used for patients with HIV who develop mild cutaneous delayed-type hypersensitivity to trimethoprim-sulfamethoxazole, with estimated tolerance rates of 75% to 90%.^{8,9} The initial rifampin dose was 1% of the treatment dose, which was approximately doubled every 24 hours for 1 week until the target dose was achieved (Table 1). Our patient tolerated rifampin for 2 weeks before his death from disseminated MAC. Given the severity of his previous reaction and onset of index symptoms 13 days after rifabutin exposure, we inferred that tolerance likely would have been sustained. Although rifampin introduction was successful in this patient, clinicians must exercise great caution in challenging a patient with a history of severe cutaneous adverse reaction to a structurally similar drug.

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