

Immunodeficiency and other clinical immunology

Use of intravenous immunoglobulin in the treatment of severe cutaneous drug reactions in patients with AIDS

Margery Sanwo, MD, Raymond Nwadiuko, MD, and Gildon Beall, MD
Torrance, Calif.

Patients with AIDS have increased frequency of severe cutaneous reactions to certain medications, and these patients often require prolonged hospitalizations because of these reactions. Some reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, appear to involve immune-mediated destruction of cutaneous tissue and therefore respond to antiinflammatory agents. Intravenous immunoglobulin has potent antiinflammatory activity. We have treated two patients with AIDS and severe drug reactions with intravenous immunoglobulin with good outcome. Corticosteroids were avoided because of the potential risk of further immunosuppression in these already immunodeficient patients. Both patients improved rapidly with intravenous immunoglobulin, and hospitalizations for treatment of these reactions were either prevented or shortened because of this treatment. Intravenous immunoglobulin therefore appears to be an effective alternative treatment for severe cutaneous drug reactions in immunodeficient patients. (J Allergy Clin Immunol 1996; 98:1112-5.)

Key words: AIDS, intravenous immunoglobulin, adverse drug reactions, Stevens-Johnson Syndrome

Patients infected with the human immunodeficiency virus have an increased incidence of adverse cutaneous reactions to certain drugs. These reactions can be severe and may manifest as persistent generalized erythroderma with fever, as Stevens-Johnson syndrome, or as toxic epidermal necrolysis. Other than supportive care, there is little proven specific treatment for these reactions. Recent evidence suggests that tissue destruction in Stevens-Johnson syndrome and toxic epidermal necrolysis is immunologically mediated.¹ Adrenal corticosteroid therapy, however, remains controversial, especially in these immunodeficient patients. Because intravenous immunoglobulin (IVIG) is effective in the treatment of a number of

Abbreviations used

IVIG: Intravenous immunoglobulin
T/S: Trimethoprim-sulfamethoxazole

autoimmune and inflammatory disorders, we treated two patients who had AIDS and severe mucocutaneous reactions to antibiotics with IVIG.

CASES

Patient 1

A 31-year-old man with AIDS, a CD4 count of 20, and a history of *Pneumocystis pneumonia* 2 years earlier was taking trimethoprim-sulfamethoxazole (T/S) for anti-*Pneumocystis* prophylaxis. He was admitted to the hospital with a diffuse pruritic rash and fever. He had conjunctivitis; edema of the hands and feet; and an erythematous rash with vesicles on the face, trunk, and extremities. Because a drug reaction was suspected, administration of T/S was discontinued. According to initial blood tests, the white blood count was 6400 with 35% bands, 44% neutrophils, and 6% eosinophils. Because of persistent fevers, the patient began receiving

From the Division of Allergy and Clinical Immunology, Harbor-UCLA Medical Center, Torrance.

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Reprint requests: Gildon Beall, MD, Harbor-UCLA Medical Center, 1000 West Carson St., Box 449, Torrance, CA 90509.

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parenteral antibiotics on the second hospital day. Radiographs and cultures failed to identify an infectious source. Possible diagnoses including toxic shock syndrome, scarlet fever, and drug reaction were entertained. Despite 5 days of treatment with antibiotics, the patient continued to have fevers over 104° F, hypotension, and rash. On hospital day 6, he was given IVIG at a dose of 400 mg/kg per day to treat possible toxic shock, because this therapy was effective in rabbit models² and in one reported patient.³ Our patient's fever quickly abated, and his condition improved, with normalization of blood pressure, decreased erythema and edema, and mild desquamation of skin (Fig. 1). Antibiotics were discontinued, and IVIG was continued for 3 days. He was discharged home, and at follow-up visit in the clinic 5 days later, his peripheral eosinophil count was 8400. The skin eruption was therefore thought to be most likely a result of T/S drug reaction rather than toxic shock syndrome. The patient received maintenance therapy of aerosolized pentamidine for anti-*Pneumocystis* prophylaxis.

Two months later, Patient 1 was readmitted to the hospital because of presumptive cerebral toxoplasmosis. He was treated with clindamycin, pyrimethamine, and folinic acid and showed clinical and radiographic improvement. Clindamycin, however, caused him abdominal distress and had to be discontinued. Because only clindamycin and sulfadiazine are well established as effective treatments for cerebral toxoplasmosis, a trial of desensitization to sulfadiazine was initiated. The protocol was adapted from previous reports of successful desensitization.⁴

Our patient initially tolerated the desensitization. After approximately 10 days of full-dose sulfadiazine therapy, the patient experienced conjunctivitis and a mild pruritic rash. Despite discontinuation of sulfadiazine, his rash continued to progress over the next 3 days. He had an ulcer in his mouth, vesicles on his upper extremities, desquamation and edema of the lips, and edema and pain of the feet. The rash, which involved his face, trunk, and extremities, had become purpuric. He was diagnosed with Stevens-Johnson syndrome. Because of the prior success of IVIG in the treatment of drug reaction in this patient, IVIG at a dose of 400 mg/kg was administered for 5 days at home. On re-evaluation after only 2 days, he was greatly improved with decreased edema of the mouth, flattening of the vesicles on the arms, and fading of the rash. After five doses of IVIG, the patient's lips and face appeared normal, the oral ulcer had disappeared, and the rash had healed.

Patient 2

A 62-year-old woman with AIDS, a CD4 count of 20, and a history of *Pneumocystis* pneumonia received maintenance therapy of daily prophylactic dapsone because of an allergy to T/S. She noted increasing pruritus of her face and chest. Because of the possibility of a drug reaction, dapsone was discontinued, and monthly aro-

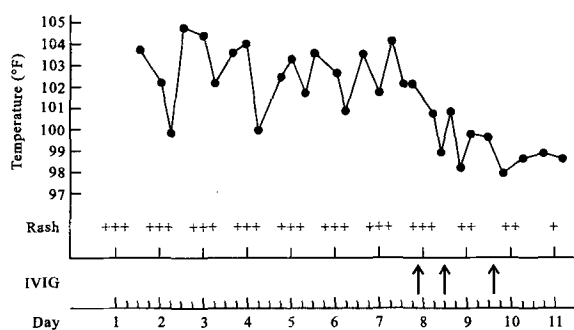


FIG. 1. Chart of symptoms and treatment for patient 1 during first episode of cutaneous drug reaction. Arrows indicate days IVIG was given. Rash was graded by severity: + + +, severe with erythema, vesiculation, moist desquamation and ulceration; + +, moderate with decreasing maculopapular rash and dry desquamation; and +, mild with dry desquamation but no erythema. Temperature plotted over time demonstrates the dramatic decline in temperature after administration of IVIG was initiated.

solized pentamidine was administered. The pruritus continued. Two months later, the patient was rechallenged with dapsone. Three weeks after re-initiation of dapsone therapy, the patient experienced high fevers, conjunctivitis, and diffuse erythroderma. Dapsone was withheld, but the patient continued to have fevers and rash and was admitted to the hospital 1 week later for evaluation.

The patient had a temperature of 102.6° F, a diffuse maculopapular erythematous rash, and conjunctivitis. There was mild desquamation of the face but no bullae. The white blood count was 9800 with 48% neutrophils, 18% bands, and 14% eosinophils. She was treated with topical steroids and antihistamines but continued to have rash and fever. Radiographs and cultures failed to identify an infectious source. On hospital day 4, approximately 10 days after dapsone was withheld, the patient still appeared to be toxic with a temperature over 104° F. IVIG was administered at a dose of 400 mg/kg daily. Twelve hours later, the patient's fever had abated, and her rash improved. She received a total of four daily dosages of IVIG and remained afebrile, with fading of her rash.

DISCUSSION

Since the HIV epidemic began, it has been observed that both HIV-positive patients and patients with AIDS are at increased risk for having cutaneous reactions to specific drugs, such as antibiotics. Sulfonamides are a common offender, and more than 50% of patients have a rash in response to these medications in some series.⁵ Drug reactions may be observed as mild self-limiting skin eruptions or severe, prolonged mucocutaneous reactions with epidermal necrosis and bullae, as in Stevens-Johnson syndrome and

toxic epidermal necrolysis. Severe reactions can result in prolonged hospitalizations, significant morbidity with internal organ involvement, superinfections, and a mortality rate of up to 50%.⁶

The pathogenesis of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis is not fully established, but there is increasing evidence that the destruction of cutaneous and mucosal tissues is immune-mediated, as a result of either immune complex-mediated or cell-mediated immune damage. In erythema multiforme, granular IgM and C3 have been observed in the upper dermal blood vessels.⁷ Also, inflammatory infiltrates in the skin consisting of T lymphocytes, monocytes, and basophils occur.¹ Keratinocytes, probably under the influence of cytokines such as interferon- γ produced by T lymphocytes, express HLA-DR antigens and adhesion molecules⁸; these molecules direct cytotoxic T cells to the keratinocytes and result in their destruction.⁹

Because of the proposed immunologic damage to skin in erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, antiinflammatory agents have been used to treat these disease states. Use of adrenal corticosteroids remains controversial, with some reports demonstrating increased mortality rates with these drugs.¹⁰ Thalidomide, which also has antiinflammatory properties possibly because of anti-tumor necrosis factor activity,¹¹ has also been tried with limited success.¹²

IVIG as a therapeutic measure appears to have dual effects. In patients with agammaglobulinemia and hypogammaglobulinemia, the passively administered antibodies to common organisms protect the patient from recurrent infections. On the other hand, in patients with autoimmune states, such as immune thrombocytopenic purpura and Kawasaki syndrome, IVIG seems to protect against excessive inflammation and further immunologic destruction. Some of the postulated mechanisms of action of IVIG therapy include:

1. Provision of anti-idiotypic antibodies to both immunoglobulin and T-cell receptors¹³
2. Inhibition of cytokine production and action and therefore downregulation of the expression of adhesion molecules¹⁴
3. Increased T-cell suppressor activity¹⁵
4. Fc receptor blockade of mononuclear phagocytes¹⁶
5. Prevention of C3 binding to target cells¹⁷

Both our patients were experiencing significant mucocutaneous reactions to antibiotics and re-

quired hospitalization. These reactions continued to progress despite discontinuation of the drugs. Because the patients both had AIDS and histories of opportunistic infections, we were reluctant to use adrenal corticosteroids in these settings. Treatment with IVIG resulted in rapid improvement of skin and mucosal lesions and resolution of constitutional symptoms and also shortened or prevented hospitalization. IVIG may be effective in these settings by inhibiting cytokine activity and therefore downregulating cell surface molecules and/or by enhancing T-cell suppressor function. Because of the good outcomes of our two patients treated with IVIG, we are planning to conduct a double-blind, placebo-controlled trial of IVIG in the treatment of severe cutaneous drug reactions in HIV-positive patients and patients with AIDS.

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