Fixed Drug Eruptions to Human Immunodeficiency Virus-1 Protease Inhibitor

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Despite numerous drug interactions that occur with human immunodeficiency virus-1 protease inhibitors, there are relatively few drug reactions. We present two patients receiving saquinavir who developed fixed drug reactions. Both reactions cleared while patients received a therapeutic dose of the medication, and in one patient a flare was seen when the patient later stopped and then restarted the medication. Although fixed drug reactions are relatively inconsequential, it is important to know that these eruptions may clear when the patient is given uninterrupted therapy of a human immunodeficiency virus-1 protease inhibitor, with only post-inflammatory hyperpigmentation.

A unique class of retrovirally encoded aspartic proteinase, which has no counterpart in mammalian cells, is essential for infectivity and proliferation of human immunodeficiency virus (HIV)-1. Thus, it is an ideal target for an antiviral therapeutic agent. In 1989, Wlodawer *et al*[1] determined the three-dimensional structure of the enzyme by X-ray crystallography and nuclear magnetic resonance spectroscopy. The visualization of protein structures by computer graphics has made receptor-based drug design feasible. In addition, receptor-based drug design allows the examination of all interactions between a bioactive molecule and a drug target (eg, steric electrostatic) at the atomic level.[1,2] It can facilitate the identification of divergent classes of compounds that react with the reactive site, but which may also have divergent biologic properties. Thus, this method of drug design permits the development of structurally distinct compounds with potentially distinct pharmacologic profiles.[1]

Early in their use in HIV-1 disease, some of these drugs have had pharmacologic problems including short half-life values; high susceptibility to hydrolysis by degradative enzymes present in the bloodstream, gut, and cells; poor absorption and oral bioavailability; rapid clearance and biliary excretion; as well as a cost that is prohibitive for many. However, the most significant problem with these drugs has been the continuing problems of most HIV-1 antiviral therapies—the rapid development of resistance.[2-6] Despite these problems, in some patients these drugs have brought about dramatic decreases in viral titers and apparent improvement in immune status.[3,4] Patients who went home to die are instead living productive lives.

Although these drugs do have side effects and interfere to a variable degree with cytochrome P-450, cutaneous drug reactions are not a significant problem.[5-8] There is an increased incidence of drug reactions in patients with HIV-1 in the presence of a crippled immune system.[9] Although the reason for this is not entirely known, it is known that the immune system is dysregulated even before there is severe depression. We present two patients with fixed drug reactions to saquinavir.

Case Reports

Case I—A 43-year-old black man with HIV-1 presented with a 2-week history of a localized pruritic erythematous papulovesicular cutaneous eruption measuring 3 × 6 cm on the lower lateral back (Figures 1 A,B). His medications included zidovudine, lamivudine, and saquinavir, and his CD4 peripheral T cell

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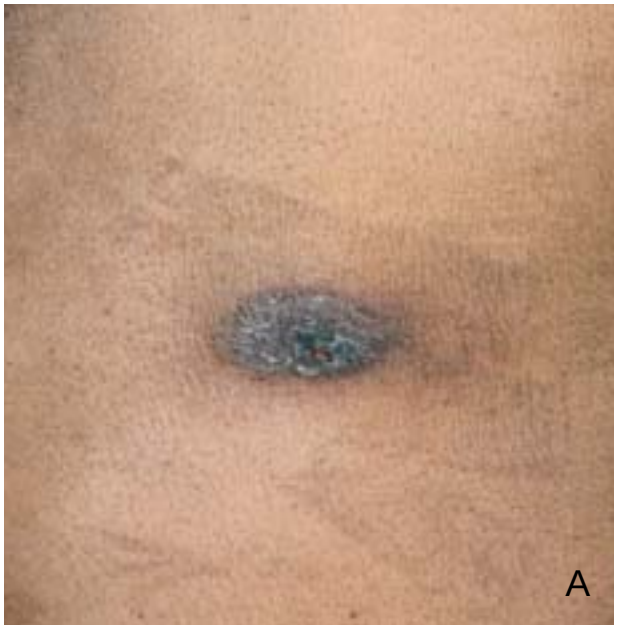
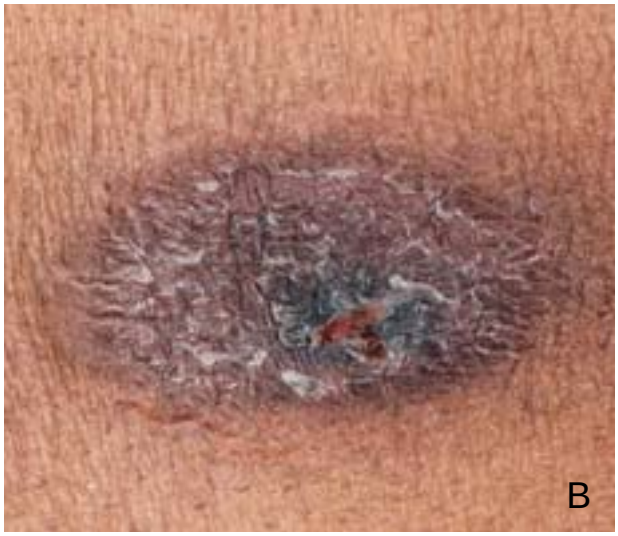
REPRINTS are not available.





FIGURES 1. A, B. Case I. A patient with human immunodeficiency virus-1 showed oval, erythematous interface eruption after starting saquinavir.

count was 271/mm^3. He had been receiving zidovudine and lamivudine for more than 9 months before the eruption, and he had started saquinavir 1 week earlier. The area was biopsied.

The saquinavir was continued, and the patient was given a potent topical steroid to use as needed for pruritus, and followed up 6 weeks later. The patient reported that he had stopped the topical steroid approximately 3 weeks earlier, and the area showed only postinflammatory hyperpigmentation. A month later, the patient started the saquinavir, and again he had a flare at the sight of the previous eruption that he treated with the topical steroids for about 2 weeks, again with postinflammatory hyperpigmentation. He remained on saquinavir for 4 more months, and then was switched to indinavir and started on stavudine and trimethoprim-sulfamethoxazole. His peripheral CD4 T cell count was 247/mm^3 at that time. The patient reported no further flares of the eruption.

Case II—A 41-year-old black man with HIV-1 presented with oval, erythematous eruptions on the right retroauricular and right lateral foot, the onset of which was probably within days of treatment with saquinavir. He had been receiving 2',3'-dideoxyinosine and lamivudine for approximately 5 months before starting saquinavir. The foot lesion was biopsied. The patient had only mild pruritus and was not given topical therapy. Over the next month, his lesions became more hyperpigmented with no residual erythema.

Histopathologic Findings

Both biopsy specimens showed similar findings with a dense interface and perivascular dermatitis. Apoptotic/dyskeratotic keratinocytes were seen within the spinous layer of the epidermis as well as at the dermal/epidermal junction (Figures 2 and 3). The inflammatory infiltrate was composed predominantly of mononuclear cells in areas showing satellitosis of apoptotic/dyskeratotic keratinocytes within the epidermis.

Immunohistochemical Findings

Immunohistochemical stains included CD 3 (CD 3/T-cell, 1:200), T cell subset CD 4 (OPD4, 1:50, DAKO), CD 20 (L26; 1:200, DAKO), CD 68 (KP1, 1:100, DAKO), factor XIIIa (1:1000, Calbiochem), MAC 387 (1:400, DAKO), and S-100 protein (S-100 PROT, 1:800, DAKO) using the ABC method with diaminobenzidine as the chromagen. CD3+ T cells were the main components within the inflammatory infiltrate, and less than 50% of these cells appeared to express OPD4. Other cells within the infiltrate included few KP-1 and MAC 387 mononuclear cells. These cell populations appeared to be distinct, as were the spindle, dendritic, and some more epithelioid S-100 protein plus mononuclear cells. MAC 387 also stained the remaining overlying spinous layers of the epidermis up to the stratum corneum.

Comments

HIV-1 protease inhibitors are the first class of drugs developed and marketed using combinatorial chemistry.[10] This involves not only three-dimensional computer modeling of the active sites, but also automated chemical synthesis, automated purification, and analysis of synthetic library products.[1,10] With software management, integration, and modeling tools, it is possible to develop drugs with much

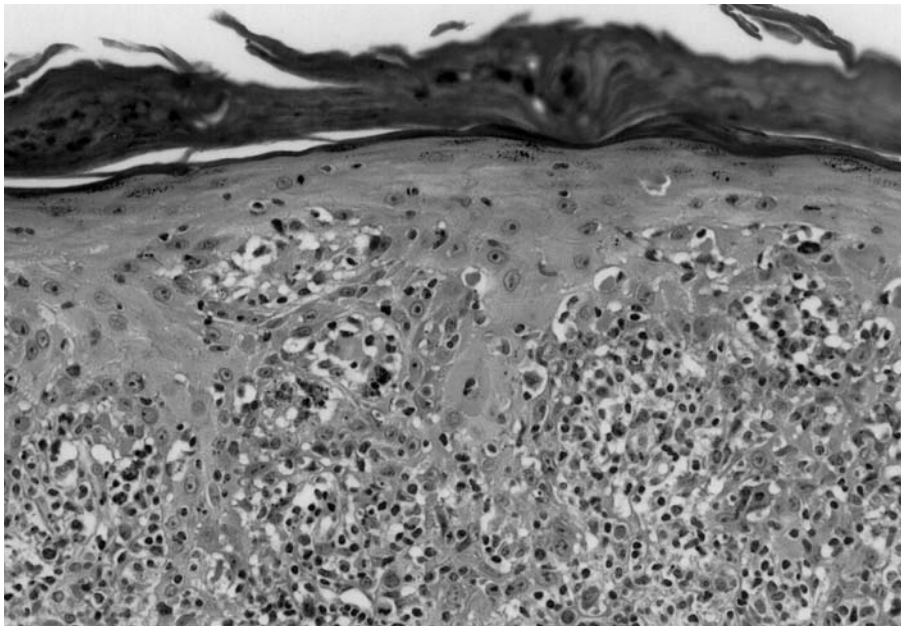


FIGURE 2. High-power view of the biopsy specimen from Case I shows an interface dermatitis with prominent apoptotic/dyskeratotic keratinocytes within the epidermis. Satellitosis of lymphocytes aside apoptotic/dyskeratotic keratinocytes is seen (H&E; original magnification, × 200).

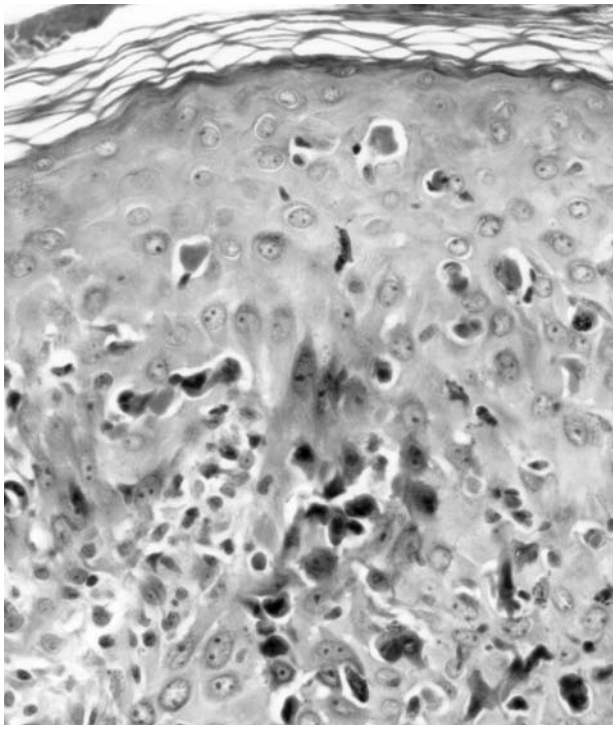


FIGURE 3. High-power view of the biopsy specimen from Case II shows an interface dermatitis and numerous apoptotic/dyskeratotic keratinocytes within the spinous layer as well as at the basal layer of the epidermis (H&E; original magnification, × 400).

greater specificity within a much shorter time than was previously possible.[10] This class of drugs has been the biggest advance to date in the therapy of HIV-1 disease, and along with the multidrug schedules has resulted in dramatic decreases in viral loads in some patients down to unmeasurable levels. However, the key to multidrug HIV-1 therapy with protease inhibitors is to maintain drug levels. Patients must take their drugs on schedules that for many are very demanding. Missing doses or "drug holidays" greatly predispose to the development of drug resistance.

The rapid development of resistance with breaks or decreases in anti-retroviral therapy means that the options for handling reactions to these medications are more limited than for drugs used in the prophylaxis for opportunistic infections. Patients developing allergic reactions to these medications are commonly given various desensitization procedures.[11-15] These procedures usually involve slowly increasing levels of the drug. However, the decreased and variable drug levels produced by these densensitization procedures would be an unsatisfactory method for handling reactions to anti-retroviral therapy, especially protease inhibitors. In general, for patients who develop reactions that are mainly maculopapular and without urticaria/angioedema, fever, new onset lymphadenopathy, elevated liver enzymes, or other evidence of systemic disease, which are not widespread, and for patients without oral involvement, we have attempted to administer regular doses.[14]

Fixed drug eruptions are localized cutaneous reactions that have histopathologic features, suggesting that they have a distinctive immunologic mechanism similar to those seen in erythema multiforme. Although early up-regulation of adhesion molecules on keratinocytes precedes the inflammatory reaction, the initiating factors and mechanism for localization are still not known.[16] It also seems unlikely that diffuse mechanisms of immune dysregulation, seen in

HIV-1 disease, would play a role in fixed drug eruptions. However, both patients did become asymptomatic with only residual hyperpigmentation when they continued on uninterrupted therapy. In addition, the first patient had a flare of his reaction site after restarting saquinavir, which he had stopped on his own. This flare also resolved with a period of uninterrupted therapy. The patient was switched to another protease inhibitor later with no further flares.

We have little experience in continuing therapy in patients who develop fixed drug eruptions. We do not know whether other such eruptions become clinically inactive with time in other patient populations, and only flare when the medication is stopped and restarted. However, in patients with HIV-1, treatment through drug eruptions should always be considered as one alternative, especially for drug eruptions that have little or no potential to be life threatening.

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