
Case Report

Amprenavir-induced maculopapular exanthem followed by desensitization in a patient with late-stage human immunodeficiency virus

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Background: Amprenavir, a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, is approved for the treatment of HIV infection in combination with other antiretroviral agents in treatment-naïve and experienced patients. Amprenavir is generally well tolerated. However, cutaneous hypersensitivity reactions to amprenavir occur in up to 28% of patients, with treatment discontinuation required in 3% of cases.

Objective: To report successful desensitization to amprenavir after the occurrence of a maculopapular exanthem in an HIV-infected patient with late-stage disease and limited antiretroviral treatment options.

Methods: Incremental doses of 0.025, 0.1, 0.25, 1, 2.5, 7.5, 25, 50, 100, 300, 600, and 1,200 mg of amprenavir oral solution were administered via percutaneous endoscopic gastrostomy tube at 20- to 30-minute intervals.

Results: The patient successfully tolerated amprenavir desensitization and has continued therapy without recurrence of rash at 19 months of follow-up.

Conclusion: Desensitization may permit the continued use of amprenavir in HIV-positive patients with a history of amprenavir-induced maculopapular eruptions who have limited alternate treatment options.

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INTRODUCTION

There is an increased occurrence of drug hypersensitivity and cutaneous reactions in human immunodeficiency virus (HIV)-infected patients compared with the general population.¹ This phenomenon has been ascribed to the numerous medications required in the long-term treatment of HIV infection, associated opportunistic infections, and other disease-related complications and to the inherent state of immune dysregulation.¹ Hypersensitivity reactions have been reported with all classes of antiretroviral drug therapy.¹ Amprenavir, an HIV-1 protease inhibitor, is approved for the treatment of HIV in treatment-naïve and experienced populations. We report a case of successful amprenavir desensitization after the occurrence of a maculopapular exanthem in a patient with late-stage HIV disease. The patient had limited antiretroviral drug therapy options for a variety of reasons, including medication formulation intolerance, drug toxic effects, and antiviral resistance.

CASE REPORT

The patient is a 40-year-old white woman with late-stage HIV disease and a nadir absolute CD4 lymphocyte count of 10 cells/mm³. Her disease course was complicated by HIV-related wasting and azole-resistant oral-esophageal candidiasis. She failed multiple trials of antiretroviral drug therapy with a variety of different treatment regimens, primarily owing to lack of ability to tolerate most of the approved drug formulations. In most cases, her intolerance manifested as an inability to ingest the drug formulation due to either incapacity to swallow capsules or a taste aversion to the liquid suspensions. Ultimately, a decision was made by the provider and patient to perform percutaneous endoscopic gastrostomy (PEG) tube placement to attempt to attain HIV control through PEG tube (vs oral) delivery of antiretroviral agents.

After PEG tube placement, the patient was started on a 4-drug regimen consisting of amprenavir (600 mg), lopinavir (400 mg)-ritonavir (100 mg), zidovudine (300 mg), and lamivudine (150 mg), all administered as oral solutions twice daily via PEG tube. Other medications administered long term, including trimethoprim-sulfamethoxazole (160 mg of trimethoprim and 800 mg of sulfamethoxazole 3 times per week) and azithromycin (1,200 mg once weekly), were changed to the equivalent oral solutions and were administered via PEG tube. Eight days after commencement of the antiretroviral drug regimen, the patient developed a moderate-to-severe, generalized, erythematous, and pruritic macu-

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lopapular eruption sparing the mucous membranes that necessitated discontinuation of all the agents. There was no fever, eosinophilia, or elevation in baseline liver function test results. The rash was treated with oral methylprednisolone, 24 mg, tapered for more than 7 days. Complete resolution of the rash occurred within 4 days. A month later, a similar maculopapular exanthem developed within several days of another challenge with amprenavir alone (600 mg of oral solution twice daily via PEG tube). This reaction occurred despite the concurrent preventive daily use of oral prednisone, 20 mg, and loratadine, 10 mg. Amprenavir treatment was discontinued, whereas prednisone and loratadine use was continued for 2 weeks to treat the rash. The exanthem resolved over several weeks after the cessation of amprenavir treatment.

Given the limited treatment options for this patient, the Allergy and Immunology Service at Yale–New Haven Hospital was consulted for possible amprenavir desensitization nearly 1 year later. Amprenavir oral solution was diluted with Ora-Sweet diluent (Paddock Laboratories Inc, Minneapolis, MN) to obtain the low concentrations required for skin testing and desensitization. Results of skin prick testing with amprenavir, 0.01 $\mu\text{g/mL}$, were negative, whereas results of intradermal testing with 0.1 $\mu\text{g/mL}$ were positive, having yielded a 7-mm wheal and a 20-mm flare. Percutaneous and intradermal testing with isotonic sodium chloride solution was nonreactive. The positive histamine control (skin prick only) resulted in a 5-mm wheal and a 20-mm flare. Amprenavir skin testing was not performed on control subjects to check for nonspecific irritation.

We developed an amprenavir desensitization protocol based on nelfinavir desensitization (Table 1).² Incremental doses of 0.025, 0.1, 0.25, 1, 2.5, 7.5, 25, 50, 100, 300, 600, and 1,200 mg of amprenavir oral solution were administered via PEG tube at 20- to 30-minute intervals. Desensitization was performed across 5½ hours in the general medicine ward of Yale–New Haven Hospital. As a precaution, an emergency

cart equipped with epinephrine, diphenhydramine, and an intubation tray was positioned at the bedside. The patient tolerated the desensitization successfully. She started receiving amprenavir oral solution, 600 mg twice daily, via PEG tube the following day. Several days later, 100 mg of ritonavir oral solution twice daily, 300 mg of tenofovir crushed tablet daily, and 300 mg of lamivudine oral solution daily were also initiated via PEG tube. The patient has continued this regimen for more than 19 months without a recurrence of rash or other manifestations of hypersensitivity.

For the first 6 months after initiation of this regimen, the patient responded well, with a decline in her HIV RNA level and an increase in her CD4 cell count. However, subsequently she had signs of treatment failure, and enfuvirtide, an inhibitor of the fusion of HIV-1 with CD4⁺ cells, was added to her regimen. She has subsequently responded well, with a 15-lb weight gain, an increase in the CD4 lymphocyte count to 159 cells/mm³, and a decline in the HIV RNA concentration to 11,800 copies/mL. She has remained free of opportunistic infections.

DISCUSSION

Cutaneous hypersensitivity reactions as a drug class effect occur most commonly with the nonnucleoside reverse transcriptase inhibitor class of antiretroviral drugs (nevirapine, 17%–24% of treated patients; delavirdine, 10%–18%; and efavirenz, 5%–10%).^{3,4} However, protease inhibitors have also been associated with exanthems. Rates of cutaneous hypersensitivity reactions of 12.5%, 4.5%, and less than 5% have been observed with ritonavir, indinavir, and nelfinavir, respectively.^{5,6} Cutaneous hypersensitivity reactions to amprenavir have been reported in up to 28% of treated patients.⁴ Typically maculopapular, pruritic, erythematous, and confluent, the rash is usually of mild-to-moderate severity in 24% of patients treated with amprenavir.⁴ However, 4% of treated patients develop grade 3 or 4 rashes (severe or life threatening), with treatment discontinuation required in 3% of cases.⁴ Stevens-Johnson syndrome occurs in 1% of patients treated with amprenavir and in 4% of patients with amprenavir-related exanthems.⁴ Associated fever and myalgias have been reported in 7% of patients with amprenavir-induced exanthems.⁷ Clinical hepatitis with elevation of the serum alanine transferase level may also occur in less than 1% of amprenavir-treated patients, with or without a concomitant rash.⁷ Whether a hepatic reaction in the absence of an associated rash is a manifestation of a drug hypersensitivity reaction is unknown.⁷

Other non-IgE-mediated adverse effects of amprenavir include nausea, vomiting, diarrhea, oral paresthesia, hyperglycemia, fat redistribution, lipid abnormalities, and possibly increased bleeding episodes in patients with hemophilia.³ Amprenavir oral solution has a high propylene glycol content compared with amprenavir capsules.³ Therefore, the oral solution is contraindicated in pregnant women, children younger than 4 years, patients with renal or hepatic failure, and patients treated with disulfiram or metronidazole.³ Symp-

Table 1. Amprenavir Desensitization Protocol*

Dose No.	Dose, mg	Volume per dose, mL	Concentration, mg/mL
1	0.025	1	0.025
2	0.1	1	0.1
3	0.25	1	0.25
4	1	1	1
5	2.5	1	2.5
6	7.5	20	0.375
7	25	20	1.25
8	50	20	2.5
9	100	20	5
10	300	20	15
11	600	40	15
12	1,200	80	15

* Doses of oral solution were administered via percutaneous endoscopic gastrostomy tube at 20- to 30-minute intervals.

toms of propylene glycol toxicity include seizures, lethargy, lactic acidosis, tachycardia, hyperosmolarity, renal dysfunction, and hemolysis.⁸

The mechanisms that underlie amprenavir hypersensitivity reactions are unidentified. The frequency of rash is greater with amprenavir than with other protease inhibitors.^{1,4} The chemical structure of amprenavir contains a sulfonamide moiety, but the likelihood of a cross-sensitivity between other sulfonamide drugs and amprenavir is unknown.⁹ Whether the sulfonamide moiety contributes to an increased incidence of rash is also not known.^{1,4} The package insert cautions against the use of amprenavir in patients with sulfonamide hypersensitivity.¹⁰ However, in practice, patients with known hypersensitivity to sulfonamides may use amprenavir, but caution is advised.⁴ Our patient did not have a history of sulfonamide hypersensitivity.

Our patient demonstrated a positive intradermal skin test reaction, but the significance of this finding is unclear. It could be due to type I IgE-mediated hypersensitivity. However, the possibility of a skin-irritant effect caused by amprenavir, the specific dose, the diluent, or preservatives cannot be excluded. Based on the clinical history of delayed maculopapular eruption, we speculate that the reaction in this patient is consistent with type IV delayed hypersensitivity. However, we did not perform epicutaneous patch testing with amprenavir. Patch testing has low sensitivity (20%–30%) to identify causative drugs in maculopapular eruptions.¹¹ Furthermore, when the concentration of a drug that produces a skin-irritant effect is unknown, patch testing is of limited utility.¹²

Other mechanisms of hypersensitivity reactions have been proposed with different protease inhibitors. In an observational study, Bonfanti et al⁵ suggested that cytochrome P450 metabolites may be involved in hypersensitivity reactions related to indinavir and ritonavir, but this hypothesis is unconfirmed. Another case report¹³ identified IgA by immunofluorescence on a skin biopsy specimen of a saquinavir-induced vasculitic rash. At the time of our patient's presentation to the Allergy and Immunology Service, the maculopapular exanthem had resolved. Consequently, biopsy of the skin lesions was not performed.

There are several additional limitations to this case. We did not perform amprenavir skin tests on control subjects, and neither did we attempt to determine the presence or quantitative titers of serum IgE antibodies to amprenavir using radioallergosorbent testing. Radioallergosorbent testing for amprenavir is not commercially available at present. In retrospect, Ora-Sweet diluent (ingredients: purified water, sucrose, glycerin, 5% sorbitol, and flavoring; buffering agents: sodium phosphate and citric acid; and preservatives: potassium sorbate and methylparaben) would have been a more appropriate choice as the negative control for skin testing instead of isotonic sodium chloride solution. Also, we did not skin test for other antiretroviral medications. Our patient was receiving multiple medications and, therefore, numerous potential inciting agents. This posed a diagnostic dilemma to

ascertain whether the patient incurred a hypersensitivity reaction to amprenavir vs other drugs or antiretroviral drug combinations. However, the patient developed a maculopapular rash when challenged again with amprenavir alone. Thus, it was highly probable that our patient had a specific hypersensitivity reaction to amprenavir.

In patients with late-stage HIV disease and limited treatment options, the management of amprenavir hypersensitivity reactions presents a challenge. Amprenavir treatment may be safely continued in patients with mild rash without systemic symptoms, such as fever and vomiting.⁴ If treatment is interrupted owing to mild rash, amprenavir may be administered again without an increased risk of severe rash.⁴ Antihistamines may relieve mild associated pruritus.⁴ However, amprenavir use should be discontinued in the setting of a moderate-to-severe rash that involves mucous membranes, fever, chills, vomiting, or intense pruritus; repeated challenge should be avoided in such cases.⁴ Antihistamines and corticosteroids are often coadministered in an attempt to treat protease inhibitor-associated exanthems, but this strategy is not always successful.^{13,14} The present case demonstrates that when such measures are unsuccessful and antiretroviral drug options are limited, amprenavir desensitization may be considered. It is unclear how desensitization works in patients with histories suggestive of non-IgE-mediated reactions, but protocols of successful desensitization or graded challenge have been reported for other antiretroviral agents.^{2,14–17}

Since the present case, therapeutic advances in available antiretroviral medications have been achieved. Fosamprenavir, a phosphate ester prodrug of amprenavir, has recently become available. The major advantage of the prodrug is decreased pill burden and once to twice daily dosing.³ Rash occurs in 19% of patients treated with fosamprenavir.³ The mechanisms underlying the occurrence of the rash are unknown. Whether cross-sensitivity for cutaneous hypersensitivity reactions exists between fosamprenavir and amprenavir is also unknown.

In conclusion, our patient successfully tolerated amprenavir desensitization. Desensitization may permit the continued use of amprenavir in HIV-positive patients with a history of amprenavir-induced maculopapular eruptions who have limited alternate treatment options. To our knowledge, this is the first case report of amprenavir desensitization. Efforts aimed at characterizing the mechanisms of amprenavir cutaneous hypersensitivity reactions are warranted given the frequency of reactions and the limited number of antiretroviral agents available for patients with late-stage HIV disease.

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