Successful Desensitization to Enfuvirtide after a Hypersensitivity Reaction in an HIV-1–Infected Man

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We report a case of successful, rapid desensitization to enfuvirtide after a hypersensitivity reaction in a man with highly drug-resistant human immunodeficiency virus type 1 infection. The patient was desensitized in a monitored intensive care unit and tolerated the rapid desensitization protocol without any serious adverse effects. This case illustrates the ability to safely desensitize patients with limited treatment options who require enfuvirtide therapy.

Case presentation. A 42-year-old white, homosexual male presented for optimization of antiretroviral therapy in March 2003. He had received a diagnosis of HIV-1 infection in 1989. His medical history also included asthma, which had never required him to be hospitalized. He had no known allergies to medications or allergens. Since initiation of the patient’s antiretroviral therapy in 1995, he had had a detectable HIV-1 viral load despite treatment with numerous antiretroviral medications. At the time of presentation in March 2003, he was taking stavudine, nelfinavir, and efavirenz. The patient reported excellent compliance with these medications. The only US Food and Drug Administration (FDA)–approved antiretroviral medications he had not previously taken were lopinavir/ritonavir, tenofovir, and enfuvirtide. The patient’s HIV-1 load was 509,890 copies/mL, and his CD4+ T lymphocyte count was 74 cells/μL (CD4+ cell percentage, 4%). HIV-1 genotype and phenotype resistance assays revealed numerous major mutations in the reverse-transcriptase and protease genomes.

The patient was enrolled in an antiretroviral salvage therapy clinical trial, during which a regimen consisting of zidovudine, lamivudine, abacavir, tenofovir, and lopinavir-ritonavir was started. A good virologic response to this regimen at week 4 was noted—the patient’s HIV-1 viral load was 29,820 copies/mL and his CD4+ T lymphocyte count was 183 cells/μL—and a decision was made to add enfuvirtide to the regimen in an attempt to fully suppress viral replication. The patient was instructed on proper preparation and administration of enfuvirtide, and he self-administered the first dose of enfuvirtide during week 9 of the protocol. Approximately 50 min after taking the first dose, he noted chest tightness accompanied by a rapid heart rate. He also had fever (temperature, 38.3°C), chills, diffuse myalgias, shortness of breath, and nausea. No rash was noted. The patient self-administered albuterol (via metered dose inhaler), with minimal relief to shortness of breath.

All of the patient’s symptoms resolved spontaneously 6 h after injection of enfuvirtide. He was instructed to not readminister the enfuvirtide. He continued to receive the other antiretroviral medications and did not experience any further adverse effects. The patient was evaluated as an outpatient by an allergy specialist (J.C.), who determined that the reaction was most likely a hypersensitivity reaction to enfuvirtide (as described in the package insert) and recommended readministration of enfuvirtide after desensitization, but only if medically necessary.

At week 33 of the protocol, lopinavir/ritonavir was discontinued and investigational tipranavir combined with ritonavir was added to the regimen because of virologic failure; the patient’s HIV-1 load was 91,045 copies/mL and CD4+ T lymphocyte count was 228 cells/μL. By week 35, his HIV-1 load had again decreased again to 1463 copies/mL with a CD4+ T lymphocyte count of 233 cells/μL. It was then decided that another attempt with enfuvirtide could be beneficial.

The patient was admitted electively to a monitored intermediate-level medical intensive care unit for the purpose of desensitization. The risks and benefits of reintroducing enfuvirtide were again reviewed with the patient, and he gave written and verbal informed consent to proceed. The patient was treated with gradually increasing doses of subcutaneous enfuvirtide. Neither antipyretics nor antihistamine medications were administered at any time during the process. The first enfuvirtide dose was 0.00625 mg administered subcutaneously, with subsequent increases in the dose at 1-h intervals (table 1). A rapid desensitization schedule was chosen to lessen the theoretical risk of developing resistance to enfuvirtide while administered at subtherapeutic levels.

Throughout desensitization, the patient was monitored for signs of respiratory distress, with his vital signs and peak ex-
piratory flow rate measured at baseline and 30 and 60 min after administration of each increased dose. The patient received all scheduled doses with no major adverse reactions noted. Tachycardia (heart rate, 120–130 beats/min) and mild headache occurred after the initial dose, but they resolved spontaneously and did not recur with subsequent doses. The patient was discharged from the hospital in stable condition on the day that the last dose of enfuvirtide was administrated (~18 h after admission). He had had no further reactions or difficulty with his therapy regimen (enfuvirtide, tipranavir-ritonavir, zidovudine, lamivudine, abacavir, and tenofovir) as of 12 weeks after desensitization, although he has experienced injection site reactions. At week 44 of the protocol, the patient’s HIV-1 load was 182 copies/mL, and his CD4+ T lymphocyte count was 344 cells/μL.

**Discussion.** In March 2003, enfuvirtide, the first of a class of drugs known as HIV fusion inhibitors, received approval by the FDA under the trade name Fuzeon (Roche Pharmaceuticals). The lack of cross-resistance to prior classes of antiretroviral medications, as well as data from clinical trials, make enfuvirtide an important option for patients in need of salvage therapy [1]. The most commonly reported side effects of this medication are local injection reactions at the sites of subcutaneous administration. Hypersensitivity reactions to enfuvirtide have been associated with this medication, but they are reported to occur in ~1% of patients (Gary L. Boggs, Roche Pharmaceuticals, personal communication). The enfuvirtide package insert states that “hypersensitivity reactions may recur on rechallenge…and have in-annual communication). In fact, the hypersensitivity reactions that occurred in 2 patients in the T-20 versus Optimized Regimen Only (TORO) clinical trials occurred days to weeks after initiation of the medication [3]. One patient developed fever and vomiting 8 days after initiation of enfuvirtide; however, rechallenge with enfuvirtide on days 17 and 22 after the first dose resulted in fever, rash, and vomiting within hours after rechallenge. The second patient with a hypersensitivity reaction in this trial developed membranoproliferative glomerulonephritis after 57 days of therapy, and rechallenge on day 223 after the first dose resulted in severe respiratory distress.

Fuzeon contains enfuvirtide, mannitol, sodium carbonate, sodium hydroxide, and hydrochloric acid. Although other antigens or medications may have been responsible for this patient’s hypersensitivity reaction, we suspect enfuvirtide was the causative agent because of the temporal relationship to the reaction. Although other medications the patient was taking have been associated with hypersensitivity reactions (e.g., abacavir), he had been taking these medications for several weeks, and the symptoms did not recur despite continuation of these medications. Also, the patient clearly stated that this hypersensitivity reaction was “far different” from his usual asthma exacerbations.

The package insert for enfuvirtide appropriately states that “therapy with Fuzeon should not be restarted following sys-temic signs and symptoms consistent with a hypersensitivity reaction” [2]. Although we believed that the patient described in this report may indeed have experienced a hypersensitivity reaction, we chose to rechallenge him with this drug due to the paucity of options for antiretroviral therapy. In conjunction with the patient’s input, we concluded that the benefits of adding enfuvirtide to his antiretroviral regimen (potentially driving his viral load to undetectable levels) outweighed the potential risks in this situation.

Enfuvirtide is also unique because it is one of the few antiretroviral medications that is available in an injectable formulation. This property allowed us to significantly dilute the medication prior to administration. One problem with exposing this patient to a diluted form of enfuvirtide was the potential emergence of resistance, which clearly and easily occurs if medication levels are subtherapeutic [4]. For this reason, we used a rather accelerated desensitization regimen, giving the full standard dose (90 mg) within 12 h after administration of the initial dose. The potential for development of resistance to enfuvirtide in this patient is yet to be determined.

Patients such as the one we describe, who are infected with complex reactions, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome [2].

Neither enfuvirtide clinical trials or postmarketing analysis have documented any immediate (i.e., occurring within hours) hypersensitivity reactions, such as the one our patient experienced (Carol Guitteri, Roche Pharmaceuticals, personal communication). In fact, the hypersensitivity reactions that occurred in 2 patients in the T-20 versus Optimized Regimen Only (TORO) clinical trials occurred days to weeks after initiation of the medication [3]. One patient developed fever and vomiting 8 days after initiation of enfuvirtide; however, rechallenge with enfuvirtide on days 17 and 22 after the first dose resulted in fever, rash, and vomiting within hours after rechallenge. The second patient with a hypersensitivity reaction in this trial developed membranoproliferative glomerulonephritis after 57 days of therapy, and rechallenge on day 223 after the first dose resulted in severe respiratory distress.

**Table 1. Enfuvirtide desensitization schedule used for a patient with a hypersensitivity reaction.**

<table>
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<tr>
<th>Time (h)</th>
<th>Enfuvirtide dose, mg</th>
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HIV with numerous antiretroviral resistance mutations, are not uncommon now. It is reported that as many as 50% of patients receiving antiretroviral therapy are infected with viruses that express resistance to at least 1 of the available antiretroviral medications [4]. Because of such limited therapeutic options and the novelty of a new class of antiretroviral medications, it is likely that enfuvirtide will play an increasing role in the salvage antiretroviral therapy. We suspect that hypersensitivity reactions may be reported with more frequency with increased use of this drug. Unfortunately, risk factors that might predict the occurrence or severity of a hypersensitivity reaction to enfuvirtide have not been identified; also, eosinophilia was not associated with clinical events suggestive of systemic hypersensitivity (Gary L. Boggs, Roche Pharmaceuticals, personal communication).

Although we cannot typically recommend the use of enfuvirtide for patients with such reactions, we provide this case presentation as a possible alternative means of rechallenging with enfuvirtide in a carefully monitored setting. As mentioned above, whether to perform such a potentially harmful rechallenge is a decision that should be made after input from the patient has been sought and discussion between the caregiver and the patient has occurred. The benefits and risks should be thoroughly considered, and alternative therapies should be strongly considered.

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References