The Safety and Efficacy of Enfuvirtide Therapy for HIV Infection in Patients with Hemophilia: A Case Series

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The treatment of patients with human immunodeficiency virus (HIV) infection and hemophilia involves unique challenges that may be addressed with novel antiretroviral classes. We describe the safety and efficacy of enfuvirtide therapy in 4 patients with severe hemophilia A. Although local skin reactions were common, neither local nor systemic bleeding worsened. Three patients achieved undetectable HIV loads with enfuvirtide salvage regimens.

The treatment of patients with HIV infection and congenital bleeding disorders involves particular challenges. These are the combined results of long duration of HIV infection; antiretroviral drug resistance following sequential antiretroviral monotherapy or dual therapy for HIV infection prior to the advent of HAART; chronic liver disease, which is associated with high rates of coinfection with hepatitis C virus (HCV) and/or hepatitis B virus; and unique susceptibility to certain toxicities, notably bleeding [1–5]. As a result, these patients’ therapeutic options may be limited and their clinical outcomes correspondingly poor [3–5]. The arrival of new classes of antiretroviral agents offers the prospect of improving patient outcomes. However, concerns regarding potential unique toxicities of novel agents in this patient group may lead clinicians to avoid their use, despite the possible benefits.

Enfuvirtide is the first of a new class of antiretrovirals known as viral entry inhibitors [6]. It acts by preventing gp41-mediated fusion of the viral envelope with the target cell membrane [7]. It is effective in combination with optimized background antiretroviral therapy, and it shows no cross-resistance with existing antiretroviral agents [8–10]. The use of enfuvirtide in patients with hemophilia has not previously been described. There is no evidence regarding its tolerability in this group, although specific concerns include the potential exacerbation of bleeding at the injection site (where local reactions are common [8,9]) and of systemic bleeding. We report on the use of enfuvirtide therapy in 4 patients with severe hemophilia A and HIV and HCV coinfection.

Case 1. A 27-year-old man was fully adherent to his fourth-line, 5-drug antiretroviral regimen. However, his viral load was detectable at 40,000 copies/mL, and he had a CD4 cell count of 162 cells/μL (CD4 cell percentage, 21%). Drug intolerances and resistance to agents across 3 drug classes limited the patient’s therapeutic options, and the treatment of his HCV infection had been deferred because of poor HIV-infection control. He experienced only occasional spontaneous muscular and articular bleeding. He initiated enfuvirtide therapy in conjunction with lopinavir, stavudine, and tenofovir therapy. He tolerated this regimen well, although he did report occasional moderate bruising at the injection site and local skin thickening. He had no increase in bleeding and maintained his normal activities, including a vacation in the South Pacific. His viral load became undetectable within 6 months, and his CD4 cell count increased to 289 cells/μL (CD4 cell percentage, 19%) after 12 months (figure 1). HCV therapy with ribavarin and pegylated IFN was introduced and was similarly well tolerated. The patient continues to receive therapy after 18 months, with a sustained HIV virological response.

Case 2. A 51-year-old splenectomized man was receiving his fifth antiretroviral regimen, but his adherence was suboptimal as the result of intercurrent depression and alcohol abuse. He had an HIV load of 39,000 copies/mL with a CD4 cell count of 162 cells/μL (CD4 cell percentage, 7%). His hemophilia was managed with prophylactic recombinant factor VIII administered 3 times per week, but frequent spontaneous hemorrhages continued to occur. Genotypic HIV drug-resistance testing revealed resistance to antiretroviral agents across 3 drug classes. The patient’s antiretroviral regimen was changed to enfuvirtide, abacavir, lamivudine, saquinavir boosted with ritonavir, tenofovir, and zidovudine. Efforts were made to maximize adherence with counselling and home nursing visits, with partial success. Over a 24-month period of follow-up, the patient experienced significant local skin reactions when receiving enfuvirtide. However, he had no local bleeding associated with enfuvirtide use, nor did the frequency and severity of his systemic bleeding increase. His clinical course was complicated when he fell while injecting himself with enfuvirtide, sustaining...
For patient 4, 6 months of follow-up data were available. UD, undetectable viral load, defined as \(<50\) copies/mL.

a fractured femur that necessitated a prolonged period of inpatient rehabilitation following an open reduction and internal fixation. During the subsequent 12-month period, the patient's viral load decreased to 4860 copies/mL, and his CD4 cell count increased to 245 cells/\(\mu\)L (CD4 cell percentage, 11%); after 24 months, the patient's viral load was 2800 copies/mL, and his CD4 cell count was 246 cells/\(\mu\)L (CD4 cell percentage, 9%) (figure 1).

**Case 3.** A 32-year-old man had chosen to interrupt his antiretroviral therapy for a period of 12 months. Following this interruption, his viral load had increased to 110,000 copies/mL, and his CD4 cell count had decreased to 135 cells/\(\mu\)L (CD4 cell percentage, 19%). HIV genotype testing showed resistance to multiple antiretroviral agents across 3 drug classes. The patient had not had an AIDS-defining illness, and his hemophilia was well controlled without prophylactic therapy. He initiated therapy with enfuvirtide in conjunction with atazanavir, lamivudine, and zidovudine following counselling. His viral load decreased to 1400 copies/mL within 3 months and became undetectable within 6 months; during the same period, his CD4 cell count increased to 264 cells/\(\mu\)L (CD4 cell percentage, 17%) (figure 1). He experienced minor local bleeding and skin thickening at the site of enfuvirtide injection, and he interrupted therapy on several occasions because of pain at the injection site. However, he experienced no increase in systemic bleeding. After 7 months, despite counselling, the patient again chose to cease therapy.

**Case 4.** A 47-year-old man with HCV-related end-stage liver failure was awaiting liver transplantation. During this time, he experienced recurrent gastrointestinal bleeding with concomitant vomiting, hepatic decompensation, and encephalopathy, despite prophylactic therapy with recombinant factor VIII administered 2 times per day. He was highly adherent to his antiretroviral therapy; however, his viral load increased from 50 copies/mL to 900 copies/mL, which was thought to be secondary to poor oral absorption of his antiretrovirals. Prior genotype testing had shown resistance to multiple antiretroviral agents. Because of the need to maintain maximal suppression of viral replication prior to transplantation and concerns regarding his oral absorption, he initiated a regimen of enfuvirtide, lopinavir, ritonavir, tenofovir, and lamivudine. He tolerated this well, with no local reactions and no increase in systemic bleeding. His viral load became undetectable within 1 month and remained suppressed after 6 months (figure 1), at which time he received a hepatic transplant. He remains well 6 months after transplantation and continues to receive the same antiretroviral regimen.

**Discussion.** This is the first reported use of enfuvirtide in patients with congenital bleeding disorders. In these patients, it was safe, well tolerated, and effective. Three of the 4 patients achieved an undetectable HIV load with the use of enfuvirtide within the salvage regimen. The major adverse effect reported was local skin reactions, but no patient experienced significant local bleeding at the injection site, despite their underlying bleeding diathesis. Similarly, no increase in the rate or severity of systemic bleeding was apparent in this small series, even in those patients with high rates of bleeding and those not receiving prophylactic coagulation factors. The major adverse event, a fall and fracture while self-injecting enfuvirtide, does illustrate the need for careful education before commencing enfuvirtide therapy, particularly because these patients may have limited mobility and osteopenia secondary to articular bleeding and joint damage [11]. The need for methodical injection technique and rotation of injection sites to minimize local bleeding must be emphasized in this group in particular. This series demonstrates that enfuvirtide, administered as part of optimized antiretroviral therapy, can be a safe and effective therapy for patients with HIV infection and hemophilia. It also confirms the promise of new classes of antiretroviral agents in improving the therapeutic outcomes and quality of life of these challenging patients.
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References