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Enfuvirtide

Updated: February 10, 2018.

OVERVIEW

Introduction

Enfuvirtide is an HIV fusion inhibitor, the first of this class of agents active against the human immunodeficiency virus (HIV). Enfuvirtide has not been associated with serum aminotransferase elevations during therapy or episodes of acute, clinically apparent liver injury.

Background

Enfuvirtide (en fue' vir tide) is relatively new antiretroviral drug that blocks the fusion of HIV to target cell, preventing viral entry and subsequent infection. Enfuvirtide is a 36 amino acid biomimetic peptide that resembles the HIV proteins that are responsible for the fusion of the virus to cell membranes and subsequent intracellular uptake. Enfuvirtide has both in vitro and in vivo activity against HIV, and several randomized controlled trials have shown that it leads to significant decline in HIV RNA levels and rises in peripheral CD4 T cell counts. Enfuvirtide was approved for use in the United States in 2003, but it has had limited use, partially because it requires parenteral administration once or twice daily. Enfuvirtide is available in single use vials that contain 90 mg/mL after reconstitution under the brand name of Fuzeon. The recommended regimen for enfuvirtide is 90 mg subcutaneously twice daily in adults and 2 mg/kg in children ages 6 to 16. Enfuvirtide is recommended only in combination with other antiretroviral agents. The only common side effects specifically linked to enfuvirtide have been injection site reactions (which can be troublesome) and eosinophilia. Regimens that include enfuvirtide have the potential to cause immune reconstitution syndrome, pneumonitis and severe hypersensivity reactions.

Hepatotoxicity

Enfuvirtide has not been reported to cause serum aminotransferase elevations at rates higher than in controls receiving similar antiretroviral therapy. No instances of clinically apparent liver injury due to enfuvirtide have appeared in the published literature. Enfuvirtide has, however, not been a widely used agent. Partially because it requires twice daily parenteral injections. Enfuvirtide is associated with rare (<1%) instances of hypersensitivity reactions with eosinophilia, rash and systemic symptoms which can be accompanied by transient serum aminotransferase elevations, but other symptoms of hypersensitivity dominate the clinical picture.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Enfuvirtide is a polypeptide and is catabolized to its constituent amino acids and rapidly cleared from the circulation. Hepatic metabolism is minimal and enfuvirtide does not affect the CYP 450 system.

Outcome and Management

If enfuvirtide hepatotoxicity occurs independent of minor aminotransferase elevations accompanying hypersensitivity reactions, it must be rare. Nevertheless, the product label for enfuvirtide mentions the possibility of toxic hepatitis and steatosis.

Drug Class: Antiviral Agents

CASE REPORT

Case 1. Serum enzyme elevations during enfuvirtide/tipranavir/ritonavir therapy.

[Modified from: Jülg B, Bogner JR, Goebel FD. Severe hepatotoxicity associated with the combination of enfuvirtide and tipranavir/ritonavir: case report. AIDS 2006; 20:1563. PubMed Citation]

A 52 year old man with long standing HIV-HBV coinfection and exposure to multiple antiretroviral agents, developed serum aminotransferase elevations 2 weeks after having tipranavir/ritonavir added to a chronic regimen of zidovudine, lamivudine and enfurvitide. Serum enzymes, which had been normal before therapy, included ALT 538 U/L and GGT 238 U/L. A liver biopsy was done that showed mild hepatitis and no steatosis. At the patient's request, enfuvirtide rather than tipranavir was stopped, and serum enzymes decreased by 50%. Serum GGT levels increased and at this point, tipranavir was stopped, whereupon all liver tests returned to normal during the next 4 weeks. Serial levels of HBV DNA were not available, but at the height of the enzyme elevations, HBV DNA was 20,000 copies/mL.

Key Points

Medication:	Tipranavir/ritonavir
Pattern:	Hepatocellular (R=5.5, based upon GGT results)
Severity:	Mild (ALT elevations without jaundice)
Latency:	2 weeks
Recovery:	4 weeks
Other medications:	Ritonavir, zidovudine, lamivudine, enfurvitide

Comment

A complex course in a patient with multidrug resistant HIV infection on five antiretroviral agents. Serum ALT levels rose after addition of tipranavir to his chronic regimen. Stopping enfuvirtide was followed by partial improvement in liver tests, but complete resolution came only with stopping tipranavir. Tipranavir with low dose ritonavir has been associated with prominent ALT elevations (at least 5 times the upper limit of the normal range) in up to 10% of patients. Thus, enfuvirtide may have promoted the hepatotoxicity of tipranavir, but the effect was minor if present at all. In this instance, the enzyme elevations did not resolve until tipranavir was stopped. In the absence of serial testing of serum enzymes, bilirubin, HIV levels, CD4 counts as well as HBV DNA (with HBeAg, anti-HBe and IgM anti-HBc), the role of an exacerbation of the underlying chronic hepatitis B caused by immune reconstitution cannot be excluded.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Enfuvirtide – Fuzeon®

DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Enfuvirtide	159519-65-0	C204-H301-N51-O64	

ANNOTATED BIBLIOGRAPHY

References updated: 10 February 2018

Núñez M. Hepatic toxicity of antiviral agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 567-91.

(Review of hepatotoxicity of antiviral medications; based upon product labeling, enfuvirtide is shown as having a ~6% incidence of "severe" drug induced liver injury).

Flexner C. Antiretroviral agents and treatment of HIV infection. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1623-1664.

(Textbook of pharmacology and therapeutics).

http://aidsinfo.nih.gov/guidelines.

(Regularly updated guidelines on use of antiretroviral agents in adults, adolescents and children with HIV infection).

Kilby JM, Lalezari JP, Eron JJ, Carlson M, Cohen C, Arduino RC, Goodgame JC, et al. The safety, plasma pharmacokinetics, and antiviral activity of subcutaneous enfuvirtide(T-20), a peptide inhibitor of gp41-mediated virus fusion, in HIV-infected adults. AIDS Res Hum Retroviruses 2002; 18: 685-93. PubMed PMID: 12167274.

(Analysis of safety and efficacy of enfuvirtide in 78 patients with HIV treated for 28 days; "no significant or clinically meaningful changes or differences between dosage groups in clinical chemistry results").

Lalezari JP, Henry K, O'Hearn M, Montaner JS, Piliero PJ, Trottier B, Walmsley S, et al.; TORO 1 Study Group. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med 2003; 348: 2175-85. PubMed PMID: 12637625.

(Large, registration trial of adding enfuvirtide to an "optimized" regimen in 501 patients with HIV infection and resistance to conventional antiretrovirals; updated combined safety analysis in 663 patients on enfuvirtide found 2 instances of hypersensitivity, but no mention of hepatotoxicity and rates of laboratory abnormalities were not different in enfuvirtide as control [optimal regimen] patients).

Lazzarin A, Clotet B, Cooper D, Reynes J, Arasteh K, Nelson M, Katlama C, et al.; TORO 2 Study Group. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Engl J Med 2003; 348: 2186-95. PubMed PMID: 12773645.

(Controlled trial of adding enfuvirtide to an "optimized" regimen in 512 patients with HIV infection and resistance to conventional antiretrovirals; updated combined safety analysis for 813 patient-years of exposure reported: "No consistent pattern was evident to suggest a definitive association of enfurvitide with any particular laboratory abnormality").

Hardy H, Skolnik PR. Enfuvirtide, a new fusion inhibitor for therapy of human immunodeficiency virus infection. Pharmacotherapy 2004; 24: 198-211. PubMed PMID: 14998221.

(Review of structure, pharmacology, mechanism of action, clinical efficacy and safety of enfuvirtide: 36-amino acid synthetic peptide derived from sequence motif of HIV protein gp41, a transmembrane protein necessary for HIV fusion to CD4 cells; found to suppress HIV in culture and in humans, but must be given by injection; metabolized to amino acids which are probably reused; large registration trials [TORO-1 and 2] demonstrated efficacy and that side effects were similar to controls except for injection site reactions [97% vs nil] and eosinophilia [10% vs 2.4%], but not associated with systemic features and no mention of hepatotoxicity).

Church JA, Hughes M, Chen J, Palumbo P, Mofenson LM, Delora P, Smith E, et al.; Pediatric AIDS Clinical Trials Group P1005 Study Team. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. Pediatr Infect Dis J 2004; 23: 713-8. PubMed PMID: 15295220.

(Analysis of efficacy and safety of up to 96 weeks of enfuvirtide therapy in 14 children with HIV infection; no mention of hepatotoxicity and no instances of liver test abnormalities above 5 times ULN).

Trottier B, Walmsley S, Reynes J, Piliero P, O'Hearn M, Nelson M, Montaner J, et al. Safety of enfuvirtide in combination with an optimized background of antiretrovirals in treatment-experienced HIV-1-infected adults over 48 weeks. J Acquir Immune Defic Syndr 2005; 40: 413-21. PubMed PMID: 16280695.

(Follow up to 48 weeks of patients in registration trials of enfuvirtide [Lazzarin 2003 and Lalezari 2003]; no mention of hepatotoxicity or rates of ALT elevations; eosinophilia in ~12.5% per year; 6 cases of hypersensitivity, 5 recurring with rechallenge and some patients developed "elevated serum liver transaminases").

Jülg B, Bogner JR, Goebel FD. Severe hepatotoxicity associated with the combination of enfuvirtide and tipranavir/ritonavir: case report. AIDS 2006; 20: 1563. PubMed PMID: 16847416.

(52 year old man with HIV-HBV co-infection developed marked increase in ALT [538 U/L] without jaundice, 2 weeks after adding tipranavir and ritonavir to a regimen of zidovudine, lamivudine and enfuvirtide, resolving in 4 weeks of stopping; possibly related to effects of enfuvirtide on drug levels, no analysis of HBV reactivation and lamivudine resistance: Case 1).

Shibuyama S, Gevorkyan A, Yoo U, Tim S, Dzhangiryan K, Scott JD. Understanding and avoiding antiretroviral adverse events. Curr Pharm Des 2006; 12: 1075-90. PubMed PMID: 16515487.

(Class wide adverse effects of antiretroviral agents include lactic acidosis for di-deoxynucleosides, rash and hepatitis for nonnucleoside reverse transcriptase inhibitors and lipodystrophy for protease inhibitors; fusion inhibitors such as enfuvirtide are well tolerated, but associated with frequent sometimes troubling injection site reactions and eosinophilia).

Raffi F, Battegay M, Rusconi S, Opravil M, Blick G, Steigbigel RT, Kraft M, et al. Combined tipranavir and enfuvirtide use associated with higher plasma tipranavir concentrations but not with increased hepatotoxicity: sub-analysis from RESIST. AIDS 2007; 21: 1977-80. PubMed PMID: 17721109.

(Analysis of clinical trial of tipranavir/ritonavir [r] vs comparator protease inhibitors/r who received enfuvirtide; tipranavir [+31%], lopinavir [+19%] and saquinavir levels [+39%] were higher in enfuvirtide treated, but rates of ALT elevations above 5 times ULN were lower in the enfuvirtide treated [6.5% vs 13%; 1% vs 2.5%; 0.9% vs 1.6%]).

Reynes J, Arasteh K, Clotet B, Cohen C, Cooper DA, Delfraissy JF, Eron JJ, et al. TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. AIDS Patient Care STDS 2007; 21: 533-43. PubMed PMID: 17711378.

(In follow up analysis of the registration trials of enfuvirtide extended to 96 weeks, no new safety issues emerged; no mention of hepatotoxicity or ALT elevations).

DeJesus E, Gottlieb MS, Gathe JC Jr, Greenberg ML, Guittari CJ, Zolopa AR. Safety and efficacy of enfuvirtide in combination with darunavir-ritonavir and an optimized background regimen in treatment-experienced human immunodeficiency virus-infected patients: the below the level of quantification study. Antimicrob Agents Chemother 2008; 52: 4315-9. PubMed PMID: 18809940.

(Among 137 patients with HIV infection receiving enfuvirtide with darunavir/ritonavir for for 24 weeks, there were 4 discontinuations and 18 serious adverse events, none were liver related; no mention of ALT elevations).

Hammer SM, Eron JJ Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, Cahn P, et al.; International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA 2008; 300: 555-70. PubMed PMID: 18677028.

(Updated recommendations on use of antiviral therapy in adults with HIV infection including use of recently approved agents: raltegravir, maraviroc and etravirine).

Wright D, Rodriguez A, Godofsky E, Walmsley S, Labriola-Tompkins E, Donatacci L, Shikhman A, et al. Efficacy and safety of 48 weeks of enfuvirtide 180 mg once-daily dosing versus 90 mg twice-daily dosing in HIV-infected patients. HIV Clin Trials 2008; 9: 73-82. PubMed PMID: 18474492.

(Comparison of once vs twice daily enfuvirtide added to an optimized regimen for 48 weeks in 61 patients with HIV infection; the two regimens had similar efficacy and safety; no mention of hepatotoxicity or ALT elevations).

Drugs for HIV infection. Treat Guidel Med Lett 2014; 12 (138): 7-16; PubMed PMID: 24457549.

(Concise review of drugs for HIV infection discusses enfuvirtide as the only fusion inhibitor approved for use in the US and mentions adverse side effects of local pain and irritation, eosinophilia, hypersensitivity reactions and increased rate of bacterial pneumonia, but does not mention ALT elevations or hepatotoxicity).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, 5 of which were attributed to antiretroviral agents, including lamivudine, zidovudine and nevirapine, but not enfuvirtide).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 12 [1.3%] were attributed to antiretroviral medications, but none specifically to enfuvirtide).

Xu F, Acosta EP, Liang L, He Y, Yang J, Kerstner-Wood C, Zheng Q, et al. Current status of the pharmacokinetics and pharmacodynamics of HIV-1 entry inhibitors and HIV therapy. Curr Drug Metab 2017; 18: 769-81. PubMed PMID: 28738768.

(Summary of the mechanism of action, pharmacokinetics and safety of enfuvirtide; no mention of ALT elevations or hepatotoxicity).

de Castro N, Braun J, Charreau I, Lafeuillade A, Viard JP, Allavena C, Aboulker JP, et al.; EASIER ANRS 138 study group. Incidence and risk factors for liver enzymes elevations in highly treatment-experienced patients switching from enfuvirtide to raltegravir: a sub-study of the ANRS-138 EASIER trial. AIDS Res Ther 2016; 13: 17. PubMed PMID: 27042193.

(Among 169 HIV infected patients on long term antiretroviral therapy who were either maintained on enfuvirtide or switched to raltegravir, serum ALT levels were more frequently elevated [above 3 times ULN] in those switched to raltegravir [7% vs 2%], but no patient developed clinically apparent liver injury and multivariate analysis suggested that tipranavir was more likely the cause of the abnormalities).