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HIV Disease and Therapy

Enfuvirtide: a new class of antiretroviral therapy for HIV infection

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Enfuvirtide is the first of a new class of antiretroviral agents recently approved for the treatment of human immunodeficiency virus (HIV)-1 infection. Present available data suggest that enfuvirtide may be a promising agent for the control of HIV infection in patients who have previously received reverse transcriptase inhibitor and protease inhibitor regimens and who are either intolerant to such drugs and/or who have gone into virological failure. Perhaps the greater limitation to the clinical use of enfuvirtide is the cost, limiting its use in the developing world.
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Introduction

The current method of reducing human immunodeficiency virus (HIV) load combines one or more of reverse transcriptase inhibitors with protease inhibitors. However despite the overall success of antiretroviral therapy (ART) in reducing the morbidity and mortality associated with HIV infection (Cole *et al*, 2003; Mocroft *et al*, 2003), many patients have progressive disease because of drug intolerance, and/or to the emergence of multi-drug resistant viral strains (Behrens *et al*, 2003; Gazzaruso *et al*, 2003; Mooser, 2003; Perez-Elias *et al*, 2003; Verhofstede *et al*, 2004). The frequency of emergence of such drug resistant HIV strains is rising (Locatelli *et al*, 2004) and particularly likely when there is suboptimal drug therapy, for example because of difficulties with patient compliance. Data from adults show that adherence to ART must be at least 95% in order to maximize the probability of maintaining an undetectable HIV (Faucher *et al*, 2004).

In recent months a new group of agents that inhibit HIV entry into CD4+ T cells have become clinically available. Unlike the aforementioned agents these drugs prevent initial entry and infection of HIV target-cells, particularly CD4+ T cells. The entry inhibitors comprise three groups: attachment-inhibitors, coreceptor-antagonists and fusion-inhibitors (Rummelein and Jager, 2003).

Enfuvirtide is the first fusion inhibitor to be approved by the US Food and Drug Administration (FDA) (Robertson, 2003) and European Commission (2003) for the treatment of HIV infection in adults and children aged 6 years and older. Enfuvirtide is a synthetic peptide derived from the naturally occurring amino acid sequence known as heptad repeat 2 (HR2) found in the HIV gp41 transmembrane glycoprotein, that normally facilitates HIV fusion with host cells (Hardy and Skolnik, 2004).

Enfuvirtide mimicks the activity of HR2 and competitively binds to the heptad repeat 1 (HR1) of gp41, preventing the interaction between HR1 and HR2 and thus inhibiting the conformational change of gp41 necessary for fusion of virions to host cells (Kilby and Eron, 2003). In addition, HR1 becomes accessible to enfuvirtide after gp41 binds CD4, whereas co-receptor binding is thought to induce the final conformational changes that lead to membrane fusion. Thus, enfuvirtide binds to a structural intermediate of the fusion process (Reeves *et al*, 2002). The *in vitro* antiviral activity of enfuvirtide has been assessed by infecting different CD4+ cell types with laboratory and clinical isolates of HIV-1. The IC_{50} (50% inhibitory concentration) for enfuvirtide in laboratory and primary isolates representing HIV-1 clades A to G ranges from 4 to 280 nm (18–1260 ng ml^{-1}) (Barretina *et al*, 2003). Enfuvirtide is similarly active *in vitro* against R5, X4, and dual tropic viruses (Derdeyn *et al*, 2000). However, it has no activity against HIV-2 (Laurence, 2002).

In vitro enfuvirtide exhibited additive to synergistic effects in cell culture assays when combined with other classes of anti-viral agents, including zidovudine, lamivudine, nelfinavir, indinavir, and efavirenz (Lalezari *et al*, 2003a,b).

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Treatment with enfuvirtide in combination with an optimized background antiretroviral regimen (e.g. reverse transcriptase plus protease inhibitors) provides significant HIV suppression and immunologic benefit in HIV-1-infected patients who have previously received multiple antiretroviral drugs (Lazzarin *et al*, 2003).

Drug resistance

Reduced susceptibility to enfuvirtide can occur, at least *in vitro*. This reduced susceptibility (i.e. virulence) by HIV is the consequence of mutations that result in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36–38 of gp41. Phenotypic analysis of site-directed mutants in positions 36–38 in an HIV-1 molecular clone showed a 5- to 684-fold decrease in susceptibility to enfuvirtide (Wei *et al*, 2002).

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects treated with enfuvirtide in combination with other antiretroviral agents. However, primary genotypic resistance to enfuvirtide is rare, regardless of subtypes or prior use of ART (Roman *et al*, 2003).

Patient acceptance

Enfuvirtide is administered parenterally, hence patients are required to become familiar with reconstituting and administering the agent, and in managing injection site reactions (ISRs) (Celano, 2003). The majority of patients will experience at least one ISR, thus they are advised on methods to help alleviate the onset and symptoms of these reactions. Patients usually encounter little difficulty with administration, and most report little impact of self-injections on their daily lives. However, instruction by nurses is important in training patients to administer enfuvirtide and to build this routine into their daily lives, thereby furthering the acceptance of enfuvirtide and promoting compliance.

Patients are advised to rotate the sites of injection thus permitting the tissues to regenerate (Maggi *et al*, 2004). Rotation of site of injections (e.g. Abdomen, thigh or arm) could potentially lead to differences in bioavailability, but this does not seem to arise (Lalezari *et al*, 2003a,b,c).

Relative to other HIV/AIDS drugs, enfuvirtide has little impact upon the activities of daily living (ADL) of patients. The majority of patients (54–96%) of one study agreeing (somewhat or strongly) that subcutaneous injections does not limit ADL. Also, in this study, patients stated that if medically indicated, they would choose to continue with this treatment mode mainly because of its effectiveness and lack of adverse side-effects (Cohen *et al*, 2002).

Adverse side effects

Enfuvirtide would seem to be safe and well tolerated (Lalezari *et al*, 2003c), ISR being the most common adverse events, affecting almost all (98%) patients (Ball and Kinchelow, 2003). These ISRs are inflammatory responses consistent with localized hypersensitivity reactions, histologically characterized as those resembling granuloma annulare. Immunoperoxidase staining indicates that the inflammatory and collagen changes are greatest in areas where enfuvirtide is deposited (Ball and Kinchelow, 2003). Other less common events include nausea, diarrhoea, dizziness, fatigue, hyperlipidemia and neuropathy (Giles, 2001).

To date, there have been no detailed reports of adverse oral side-effects of enfuvirtide. Dysgeusia, and occasional lip and tongue swelling related to allergic reaction following administration of enfuvirtide have been mentioned, but no other details are currently available.

Conclusion

Present available data thus suggest that enfuvirtide may be a promising agent for the control of HIV infection in patients who have previously received nucleoside reverse transcriptase inhibitor (NRTI), non-NRTI and protease inhibitor regimens and who are either drug intolerant or have not experienced substantial decrease in HIV viral or marked increase in CD4+ T cell count. Enfuvirtide should ideally be used while there are still other drug options available to combine with enfuvirtide in an effective therapy regimen. Specific adverse oral side-effects of this drug have yet to be described in detail. Perhaps the greater limitation to the clinical use of enfuvirtide is its cost (around US$ 25 000 per patient per year), and thus it is unlikely to be available for the majority of patients already receiving ART in the developing world.

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