HIV fusion inhibitors: a review

Mark Boyd and Sarah Pett, Infectious Diseases Physicians, Therapeutic and Vaccine Research Program, National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, and the HIV, Immunology and Infectious Diseases Clinic Services Unit, St Vincent's Hospital, Sydney

Summary

Combination antiretroviral therapy has revolutionised the management of HIV infection. A life expectancy of more than 35 years is now realistic for a young person diagnosed with HIV infection in Australia. Despite this success, antiretroviral regimens predictably fail in a proportion of patients. There is therefore a continuing research effort to discover, develop and deliver new antiretroviral drugs. HIV fusion inhibitors represent a novel class of antiretroviral drugs and enfuvirtide is the first drug within this class to be approved for use in Australia.

Key words: antiretroviral drugs, enfuvirtide, HIV/AIDS.

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Introduction

There are several classes of antiretroviral drugs, each with a different site of action in the HIV life cycle.[1] Combination antiretroviral therapy for treating HIV infection has provided potent and durable reductions in HIV plasma viral load.[2] The resultant immune reconstitution has led to a return to health for many HIV-infected individuals.

Despite its success, sequential combination antiretroviral therapy fails in a proportion of patients who develop multidrug resistant virus. Such patients are at increased risk of HIV disease progression. As a consequence, there is an ongoing need to find new drugs that can be added to the therapeutic armamentarium and provide 'salvage therapy' for those who have failed previous regimens. One such example is enfuvirtide, the first available and only licensed HIV fusion inhibitor.

HIV fusion

The scientific investigation of the life cycle of HIV has been an area of intense research since the first description of the virus in 1983. In order to gain entry to the intracellular human machinery, which all viruses require for replication, the virus must fuse with the human cell membrane. This occurs in a complex sequence of events following attachment of the HIV-1 surface glycoprotein 120 (gp120) binding site to human cells expressing CD4 receptor molecules (for example T-lymphocytes). After binding, gp120 changes shape to allow the viral glycoprotein 41 (gp41) to form a pore in the membrane through which the virus can enter (Fig. 1).

How enfuvirtide was developed

Enfuvirtide is a synthetic 36-amino acid peptide analogue. It binds to the first heptad repeat region of gp41, disrupting interactions with the second heptad repeat region of gp41, thereby interrupting the fusion reaction and preventing the virus from infecting the host cell.

Interestingly, the development of enfuvirtide emerged from a serendipitous observation made during epitope-mapping experiments for HIV vaccine development. Synthetic peptides derived from the HIV envelope gp41 produced an antiviral effect when incubated with HIV virus and human T cells. Subsequent understanding of the fusion process, and how envelope glycoproteins interact, led to an appreciation of how these peptides inhibit the fusion of HIV with the human cell membrane, and interrupt the HIV life cycle.[3]

Pharmacology

Early studies of enfuvirtide showed predictable pharmacokinetics as well as plasma concentrations *in vivo*. However, enfuvirtide cannot be administered orally as it is a large peptide which is broken down in the digestive tract before absorption. It is therefore given twice daily by subcutaneous injection. As a peptide it is catabolised and does not rely on hepatic metabolism so has little potential for clinically meaningful drug-drug interactions.

Clinical studies

The pivotal phase III studies of enfuvirtide (TORO 1 and TORO 2) were conducted in two separate international multicentre randomised controlled trials.[4,5] These studies had almost identical designs, and differed only in the minimum length

Fig. 1

Simplified diagram of HIV fusion and entry into CD4 cells

HIV entry can be divided into several discrete steps: (A) Attachment of the viral glycoprotein 120 (gp120) to the CD4 receptor. (B) Conformational changes of gp120 which expose structural elements on the V3 loop that bind to the chemokine receptors (e.g. CCR5). (C) A structural rearrangement in glycoprotein 41 (gp41) is induced which inserts a hydrophobic fusion peptide region into the target cell membrane bringing the virus and cell membrane in close apposition to initiate fusion. (D) The virus can then enter the host cell. Enfuvirtide inhibits fusion by binding to gp41 and preventing the formation of a pore in the CD4 membrane.

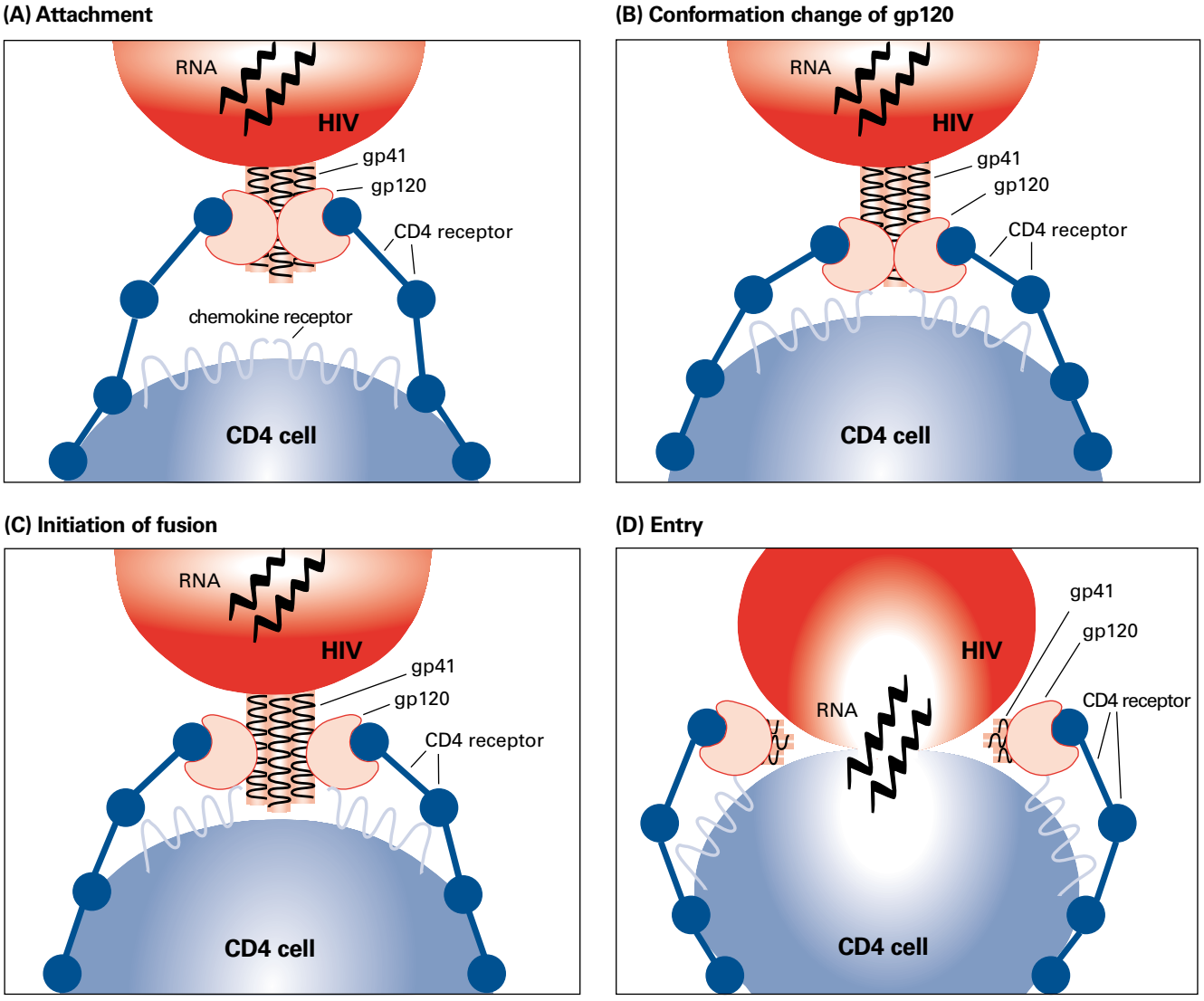

Figure adapted with permission from Hardy H, Skolnik PR. Enfuvirtide, a new fusion inhibitor for therapy of human immunodeficiency virus infection. Pharmacotherapy 2004;24:198-211.

of previous exposure to antiretroviral therapy (six and three months for TORO 1 and 2 respectively). The patient population had been exposed to, and/or had documented resistance to, at least one drug within the three available antiretroviral therapy classes at the time of enrolment. These classes were the protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors and the non-nucleoside reverse transcriptase inhibitors. Patients were randomised 1:2 to receive either an 'optimised background regimen' consisting of 3–5 drugs selected on the basis of the patient's history and viral drug resistance testing, or the optimised background regimen plus enfuvirtide.

In both studies the patients on enfuvirtide did significantly better than those who received only the optimised background

regimen, with combined viral load reductions of –1.48 versus – 0.63 $\log_{10}$ copies/mL and CD4+ T cell gains of 91 versus 45 cells/mm^3 after 24 weeks of therapy. Licensing approval was based on these studies. Prolonged follow-up showed that optimised background regimen plus enfuvirtide provided a durable response in 24-week responders out to 48 weeks. The week 12 response predicts durable virological suppression at weeks 24, 48 and 96.[6]

Sub-group analyses of the combined TORO databases suggested that the predictors of better response to optimum background regimen plus enfuvirtide were higher baseline CD4+ T cell count (more than 100 cells per mm^3), baseline viral load of less than 100 000 copies/mL, exposure to less than 10 antiretrovirals and finally, the combination of enfuvirtide with at least two other active antiretrovirals.[6] These findings emphasised the critical importance of using enfuvirtide in combination with other active drugs, and has been reinforced by subsequent experience.[7]

Safety and tolerability

Hypersensitivity reactions manifesting as rash, fever, chills, nausea and vomiting which re-emerge on challenge have been described, albeit rarely. Enfuvirtide appears not to have any overlapping long-term toxicities with other commonly used antiretrovirals (including the HIV lipodystrophy syndrome).

There was an association with an increased risk of bacterial pneumonia reported in the TORO studies in those receiving enfuvirtide compared to those who did not (4.7 vs 0.6 bacterial pneumonia events per 100 person years). However, an analysis of the patients remaining in the study at 96 weeks (that is, patients originally randomised to receive enfuvirtide with continuing follow-up and patients initially randomised to placebo who accessed enfuvirtide after week 48) showed no increase in the incidence of pneumonia (< 2%), which remained unchanged over time. From this the authors suggest that the risk of pneumonia was independent of receiving enfuvirtide.[8]

Injection site reactions

The commonest adverse effect of enfuvirtide is injection site reaction which is experienced by more than 90% of those injecting enfuvirtide. Reactions are generally characterised by one or more of the following, such as local pain, erythema, pruritis, induration, ecchymosis, nodules and cysts. Excisional biopsy studies have shown inflammatory infiltrates consistent with a localised reaction. We have observed in our unit scleroderma-like skin changes with chronic use of enfuvirtide (more than one year exposure).

The need for twice-daily injections has proven a substantial barrier to the acceptance of enfuvirtide by prescribers and patients. In those who do access the therapy, the occurrence of local injection site reactions, while infrequently treatment limiting, is associated with a degree of treatment fatigue.[9] Recently a gas-powered, needle-free injector device has been trialled as an alternative drug delivery mechanism. Early experience in observational studies suggest that the needle-free injection system might be associated with less severe injection site reactions and that the pharmacokinetics are similar to those achieved by needle delivery.[10] However, a recent randomised controlled trial conducted in enfuvirtide-experienced patients found that the needle-free injector device made no major impact on injection site reactions compared to delivery through a standard 27-gauge needle.[11] In October 2007, Roche/Trimeris announced that it was withdrawing its application with drug regulators to market enfuvirtide in tandem with the device.

Discontinuations due to adverse effects

Surveillance of the 997 patients entered into the TORO trials through the first 24 weeks showed that 8.9% of patients in the enfuvirtide group discontinued antiretroviral therapy due to adverse events as opposed to 3.6% receiving the optimum background regimen alone. Enfuvirtide injection site reactions accounted for approximately half of the discontinuations.

Resistance to enfuvirtide

As with all antiretroviral therapy, resistance to enfuvirtide may develop, particularly when viral suppression is not optimal. Resistance to enfuvirtide is mediated by amino acid substitutions within the first heptad repeat region of gp41 at amino acids 36 to 45. The mutations confer significantly reduced binding of enfuvirtide to this region and result in decreased antiviral activity *in vitro*.

Resistance emerges fairly rapidly in patients experiencing virological failure with an enfuvirtide-containing antiretroviral regimen, and is associated with the return of the plasma HIV load toward baseline within a few weeks. It seems therefore that enfuvirtide has a relatively low genetic barrier to the development of resistance.

The degree to which enfuvirtide exerts continued antiviral activity in the presence of incomplete viral suppression and drug-resistance mutations has been investigated. In a small study of 25 patients, enfuvirtide interruption was associated with an immediate but limited increase in plasma viral load, suggesting that despite resistance enfuvirtide may still exert partial antiviral activity. The clinical significance of these observations remains undefined.[12]

The future of fusion inhibitors

The use of enfuvirtide has been hindered by a limited acceptance of the twice-daily injection regimen. Unfortunately, a study of the use of once-daily enfuvirtide showed a trend towards a weaker antiviral effect compared with the twice-daily regimen. Hence, there have been renewed efforts to develop the next generation of fusion inhibitor peptides.

Until recently a candidate peptide (TRI-1144) was being advanced as a pre-clinical product in another collaboration between Trimeris and Roche. However, in mid-March 2007 Roche announced that they had returned all rights to joint patents and intellectual property for next-generation fusion inhibitors, including TRI-1144, back to Trimeris. This action inevitably calls into question the future development of the class.

The chemokine (C-C motif) receptor 5 (CCR5) antagonists are a new class of HIV entry inhibitors now in phase III trials, with an expanded access program currently available. Registration in Australia is expected in the near future. These drugs inhibit viral entry by blocking the interaction between the co-receptor CCR5 and HIV. Unlike the fusion inhibitors, they are host-directed not viral-directed drugs. There is interest in the potential synergistic effect of administering an HIV fusion inhibitor with a CCR5 antagonist, and this is currently under investigation.

Conclusion

While the use of enfuvirtide is associated with substantial improvements in virological, immunological and clinical outcomes in treatment-experienced patients, particularly when combined with antiretroviral drugs, its uptake has been limited because of the need for delivery by twice-daily subcutaneous injection. However, there is no doubt that the drug offers potent antiretroviral activity and its use should be strongly considered in patients with multiple regimen failures as a component of a new regimen aimed to effect full and durable virological suppression.

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Dr Boyd has received funding from Roche for attendance at an international conference, and has acted as a paid adviser. Dr Pett has attended a weekend conference funded by Roche.

Self-test questions

The following statements are either true or false (answers on page 83)

3. Resistance to enfuvirtide has not yet been reported.
4. Most patients have a local inflammatory reaction to enfuvirtide injections.

Therapeutic Guidelines: Emergency

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