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Enfuvirtide

Prop INN, USAN

Anti-HIV
Fusion Inhibitor

Pentafuside
DP-178
R-698
T-20

N-Acetyl-L-tyrosyl-L-threonyl-L-seryl-L-leucyl-L-isoleucyl-L-histidyl-L-seryl-L-leucyl-L-isoleucyl-L-glutamyl-L-glutamyl-L-seryl-L-glutaminyl-L-asparaginyl-L-glutaminyl-L-glutaminyl-L-glutamyl-L-lysyl-L-asparaginyl-L-glutamyl-L-glutaminyl-L-glutamyl-L-leucyl-L-leucyl-L-glutamyl-L-leucyl-L-aspartyl-L-lysyl-L-tryptophyl-L-alanyl-L-seryl-L-leucyl-L-tryptophyl-L-asparaginyl-L-tryptophyl-L-phenylalaninamide

$C_{204}H_{301}N_{51}O_{64}$
Mol wt: 4491.9150
CAS: 159519-65-0
EN: 217659

Abstract

Enfuvirtide is the first of a new class of antiretroviral agents that block HIV-1 entry into the host cell by binding to the gp41 subunit of the HIV Env glycoprotein. *In vitro* studies have revealed that enfuvirtide decreases viral p24 production and HIV-1 RNA levels, and *in vivo* it decreases HIV-1 RNA copy number and the mean viral load. The pharmacokinetic profile of the drug suggests that twice-daily administration is a good therapeutic regimen. Clinical studies conducted to date have confirmed that enfuvirtide is an effective and safe drug for treating both adult and pediatric HIV-1 positive patients, with only mild or moderate adverse effects being reported.

Synthesis

The synthesis of enfuvirtide can be performed by a general solid-phase peptide synthesis methodology using 9-fluorenylmethoxycarbonyl (Fmoc) chemistry on an automatic synthesizer using Rink resin. When an Applied Biosystems 431A peptide synthesizer is used, a “Fast Moc” protocol is followed employing HBTU and HOBt in DMF as coupling agents. First residues are double coupled to the resin and subsequent residues are single coupled. When all the couplings have been completed, the peptide is blocked at the C-terminus by an amide group and at the N-terminus by an acetyl group introduced by acylation with acetic anhydride. The peptide is cleaved from the resin by treatment with trifluoroacetic acid, water, thioanisole, ethanedithiol and crystalline phenol as carbocation scavengers. Finally, the crude peptide is purified by reverse-phase HPLC (1-3).

Enfuvirtide can also be obtained through a convergent peptide synthesis strategy: The peptide fragments are preferably synthesized using solid-phase peptide synthesis techniques employing either 2-chlorotrityl chloride resin or 4-hydroxymethyl-3-methoxyphenoxybutyric acid resin. For each fragment, the first amino acid is introduced by means of DIEA in dichloroethane (DCE)/dichloromethane (DCM) or DCE/DCM/DMF and the next amino acids are coupled using a standard Fmoc protocol employing HOBt, HBTU and DIEA in NMP; piperidine/NMP is used for Fmoc removal. The different peptide fragments can be cleaved from the resin under different conditions, *e.g.*, AcOH or 1-2% TFA in DCM. Alternatively, the fragments can be constructed using a combination of solid-phase and solution-phase synthesis techniques. The different peptidic fragments are condensed in solution using HOAt and HBTU in DMF in the presence of DIEA. Finally, enfuvirtide is obtained by *N*-terminal acetylation with Ac_2O in DMF/pyridine, followed by side-chain deprotection with TFA/water/dithiothreitol and chromatographic purification (MPLC) (4).

Introduction

The HIV envelope glycoprotein (Env) is a trimeric protein of noncovalently associated gp120/gp41 heterodimers that plays a crucial role in the entry of HIV particles into host cells. Binding of this viral gp120/gp41

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glycoprotein complex to the cellular transmembrane protein CD4 of T-helper cells and macrophages induces a conformational change in the gp120/gp41 complex, which then binds to the so-called "coreceptor" (another cellular transmembrane glycoprotein that is usually a chemokine receptor). This new conformational change results in the fusion of the viral and host cell membranes, which allows the viral core to enter the cytoplasm. The core is then uncoated and the viral nucleoprotein complex is exposed and targeted to the host cell nucleus, where viral RNA is reverse-transcribed into linear double-stranded viral DNA that is then integrated into the host cell genome. The integrated DNA is used as a template for the synthesis of additional viral RNA molecules and proteins, and eventually viral particles assemble inside the cytoplasm and are released by budding from the cell membrane (5).

Treatment for HIV-1 infection has focused on blocking the viral life cycle. Inhibition of viral DNA synthesis is a major target for antiretroviral drugs, which either bind to and inactivate the viral reverse transcriptase (non-nucleoside inhibitors, such as nevirapine) or inhibit elongation of viral DNA strands (nucleoside analogues, such as AZT). Other antiviral drugs (*e.g.*, indinavir) act by inhibiting the viral protease that is necessary for cleaving the Gag and Gag-Pol polyproteins and thus rendering mature, infectious, viral particles (5). The discovery of viral mutants that are resistant to these agents (either alone or combined with other antiviral drugs) together with other factors such as long-term toxicities, pill burdens and adherence to treatment issues, have prompted the search for new drugs that have an effect on other stages of the viral cell cycle.

Virus entry depends on the gp120/gp41 complex attaining a final conformation that is crucial for the fusion of viral particles to host cells. Binding of the trimeric gp120/gp41 complex to the chemokine receptor results in the exposure of the trimeric-coiled coil formed by the N-terminal heptad repeat region (HR1) of the viral gp41 subunit, which is then inserted into the host cell membrane. Then, the C-terminal heptad repeat region (HR2) of the viral gp41 subunit folds back into the grooves of the coiled coil to form a thermodynamically stable six-helix bundle that provides the energy necessary for membrane fusion (6, 7). Prevention of this final conformational change is an attractive target for antiviral drug intervention, as it may prevent infection of new cells and ultimately reduce virus levels in cell reservoirs. This may be achieved by following two strategies: (i) drugs that bind to intermediate conformations of the gp120/gp41 complex, thus rendering them incapable of binding to chemokine receptors; and (ii) chemokine antagonists. Table I shows a list of virus entry inhibitors currently being developed for the treatment of HIV infection.

Enfuvirtide (also known as pentafuside, T-20 or DP178) is currently the primary fusion inhibitor that is being jointly developed by Trimeris Inc. and Roche Pharmaceuticals. It is a synthetic 36-amino acid peptide derived from the HIV-1 gp41 protein that mimics the HR2 domain. Enfuvirtide is a selective and potent inhibitor of HIV-1 fusion (IC_{50} = 1 ng/ml) and infection (IC_{50} = 80 ng/ml) that binds to the HR1 trimeric-coiled coil and prevents the formation of the HR1-HR2 six-helix bundle, thus preventing fusion of the viral particle with the host cell (8-12).

Pharmacological Actions

In vitro *studies*

The study of virus-mediated cell-cell fusion using experimental models such as syncytium formation between cells expressing HIV-1 envelope proteins and uninfected CD4-expressing target cells has provided useful information on agents that inhibit virus entry. These studies confirmed that enfuvirtide is an extremely potent inhibitor, giving an IC_{90} value of 1.4 ng/ml and a 90% decrease in syncytium formation at concentrations 100-1000 times lower than other gp41-based peptide inhibitors. Enfuvirtide also inhibited infection of peripheral blood mononuclear cells (PBMCs) by cell-free HIV-1 virus, although at concentrations higher than those needed to achieve similar levels of inhibition in the cell-cell fusion experiments (13).

Following *in vitro* HIV-1 infection, production of viral p24 antigen was 500 times lower and HIV-1 replication was more than 20 times lower in cultures of a T-helper cell line transfected with a retrovirus vector that expressed membrane-anchored enfuvirtide on its cell surface than in control cell cultures (14). The addition of enfuvirtide to human monocyte-macrophage cultures also inhibited p24 production (IC_{50} = 3 μg/ml, IC_{90} = 10 μg/ml) and decreased HIV-1 RNA levels (IC_{50} = 2 μg/ml, IC_{90} = 11 μg/ml) in the culture supernatant (15).

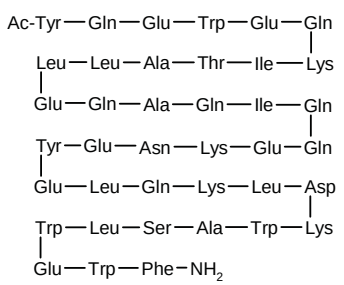
Evidence has been presented suggesting that the coreceptor used by HIV-1 for entering into the host cell may influence the inhibitory effect induced by enfuvirtide. Virus isolates that use CCR5 as coreceptor present mean IC_{50} values of 0.3-0.8 $\log_{10}$ times higher than virus isolates that use CXCR4 as coreceptor (16-20). It has been suggested that differences in the affinity of the gp120-coreceptor interactions may be the cause of the relative resistance of CCR5 viruses to inhibition by enfuvirtide compared with CXCR4 viruses (20). Further studies are currently under way to confirm the relationship between viral affinity for coreceptors and sensitivity to fusion inhibitors.

Other studies have focused on the combination of enfuvirtide with other drugs, especially those that affect binding of the gp120/gp41 complex to the host cell. The synergistic effect of combining enfuvirtide with AMD-3100, an inhibitor of binding of HIV-1 to chemokine receptor CXCR4, was studied in human PBMCs infected with an HIV-1 clinical isolate. The HIV-1 inoculum was susceptible to both drugs when these were added simultaneously with the viral inoculum, and the IC_{50} values measured were 0.10 ± 0.05 μg/ml for enfuvirtide and 0.19 ± 0.18 μg/ml for AMD-3100. Moreover, the combination

Table I: HIV entry inhibitors in clinical and preclinical development (from Prous Science Integrity®).

Drug Name	Organization	Mechanism of Action	Phase
1. Enfuvirtide	Trimeris/Roche	Fusion inhibitor	III
2. Dextrin Sulfate	ML Laboratories		II/III
3. FP-21399	Lexigen	Fusion inhibitor	II
4. PRO-542	Progenics	Fusion inhibitor	II
5. T-1249	Roche/Trimeris	Fusion inhibitor	II
6. SCH-351125 (SCH-C)	Schering-Plough	Chemokine CCR5 antagonist	I
7. TAK-779	Takeda	Chemokine CCR5 antagonist	I
8. UK-427857[1]	Pfizer	Chemokine CCR5 antagonist	I
9. AMD-8664	AnorMED	Chemokine CXCR4 antagonist	Preclinical
10. *O*-(2-Hydroxypropyl)-β-Cyclodextrin	Cyclodextrin Technologies Development		Preclinical
11. SCH-350634	Schering-Plough	Chemokine CCR5 antagonist	Preclinical
12. SCH-D[1]	Schering-Plough	Chemokine CCR5 antagonist	Preclinical
13. 5-Helix[1]	Howard Hughes Medical Institute	Fusion inhibitor	Biol. Testing

(1)



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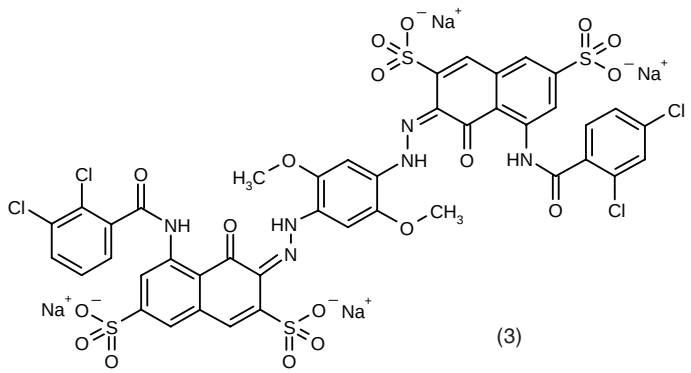
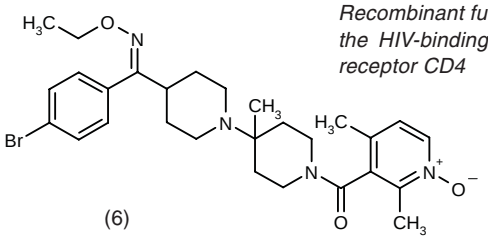


(3)

Recombinant fusion protein incorporating IgG2 and the HIV-binding region of the human cell-surface receptor CD4

(4)



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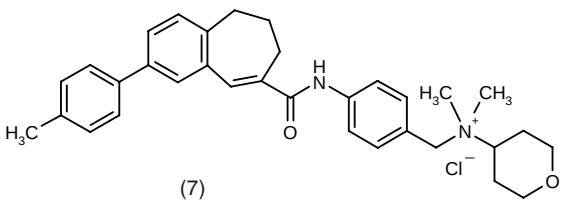

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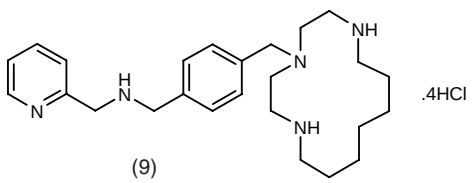
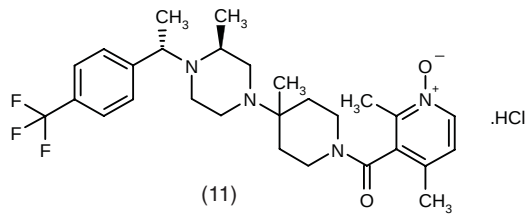


.4HCl

(9)



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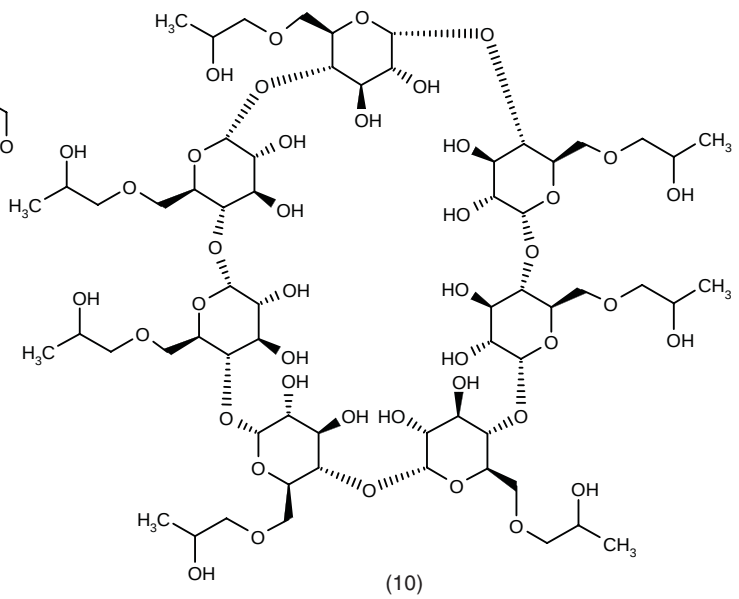

(10)

[1]Structure not yet detected

index (CI) values measured for this drug combination ranged between 0.62 and 0.02 at different drug concentrations. Taking into account that synergy is defined as CI < 1, additive effect as CI = 1 and antagonism as CI > 1, these results suggested a very strong synergistic effect for the combination of AMD-3100 and enfuvirtide on the inhibition of virus entry into human PBMCs (21). CI values of 0.11-0.68 have also been reported for the combination of enfuvirtide with the CCR5 chemokine receptor inhibitor TAK-779 (22). Cell-cell fusion experiments (with $CD4^+$ target cells and HeLa cells expressing viral protein Env) and virus-cell fusion experiments (with Hela $CD4^+$ $CCR5^-$ cells and HIV-1 Env^- viruses coated with Env protein from two different HIV-1 isolates) also confirmed the presence of a synergistic effect for enfuvirtide plus PRO-542, a CD4-immunoglobulin fusion protein (23). Finally, the combination of enfuvirtide with drugs that do not affect virus entry, such as reverse transcriptase and protease inhibitors, also had synergistic effects on the inhibition of HIV-1 replication. CI values of 0.3-0.7, 0.4-07 and 0.5-06 have been reported for enfuvirtide in combination with AZT or 3TC, indinavir and nelfinavir, respectively (24). DAPD, a nucleoside analogue active against HIV-1 isolates less susceptible to other reverse transcriptase inhibitors, also showed synergy when combined with enfuvirtide (25).

In vivo *studies*

Studies conducted in mice have confirmed the ability of enfuvirtide to inhibit HIV-1 replication *in vivo*. The HuPBMC-SCID mouse model of HIV-1 infection, which consists of SCID mice that have been intraperitoneally primed with adult human PBMCs, has been extensively used in these and other studies with different antiviral agents. HuPBMC-SCID mice were infected with 1000 $TCID_{50}$ HIV-1 9320 and intraperitoneally treated with either 2, 20 or 200 mg/kg/day of enfuvirtide. After 1 week of treatment, HIV-1 infection was determined by quantitative coculture with human PBMC blasts. Dose-dependent decreases in RNA copy number and infectious particles were found in blood, splenocytes, peritoneal cells and lymph nodes. No infectious HIV-1 particles were recovered from any of the tissues of animals treated with the highest dose (200 mg/kg/day), although low HIV-1 RNA levels were found in some of these animals (15, 26), and the mean viral load in the lymph nodes of animals treated with 200 mg/kg/day decreased to 8.2 copies/1 million cells compared with 17 million copies/1 million cells when a saline treatment was administered (27).

Pharmacokinetics

Biodistribution studies performed in rodents showed that enfuvirtide easily penetrates the lymphatic system, and maximum enfuvirtide concentrations were achieved in the lymph nodes 30 min after i.v. injection (26). Its half-life in circulation was 2.4 h and drug levels remained above the IC_{50} for 6 h (28). No detectable degradation of enfuvirtide was found *ex vivo* after incubation in plasma at 37 °C for 4 h. Clearance of enfuvirtide from plasma followed a biexponential process. The distribution phase half-life of enfuvirtide was 15 min following s.c. and i.m. administration, and the elimination phase half-life was approximately 2.5 h (29, 30).

Pharmacokinetic studies conducted in primates confirmed the results obtained in rodents and also that enfuvirtide is distributed largely to blood and lymphatic fluid (26, 30). Plasma AUC values in primates varied depending on the amount of enfuvirtide administered by s.c. injection (29). The elimination phase half-life was higher than 3 h after i.v., i.m. and s.c. administration, and the relative bioavailability of enfuvirtide has been estimated to be above 70% when administered s.c. or i.m. (31).

Clinical studies conducted with enfuvirtide have also provided useful information on the drug's pharmacokinetics in humans. Twice-daily i.v. administration of enfuvirtide for 14 days resulted in maximum observed concentration, maximum theoretical concentration and area under curve values that increased with drug dose. The median half-life in circulation was 1.83 h, and no significant differences were found between single-dose and continuous administration (32) (Table II). The pharmacokinetics of 100 mg and 50 mg CO_3 formulations of enfuvirtide were similar (33). A pharmacokinetic study conducted in children 3-12 years of age revealed that the s.c. administration of a 60 mg/m^2 dose of enfuvirtide resulted in 12-h trough plasma levels above a target level of 1 μg/ml, which was considered to be necessary for effective viral suppression (34).

A recent open-label, randomized, 4-way crossover study analyzed the pharmacokinetics of enfuvirtide in 12 HIV-1 infected patients who received 4 single doses of the drug separated by a 1-week washout period. The doses administered were 90 mg i.v. and 45, 90 and 180 mg s.c., and blood samples were collected up to 48 h after drug administration. The enfuvirtide plasma concentration-time course after s.c. administration was indicative of an inverse Gaussian density function input model linked to a two-compartment open distribution model with elimination from the central compartment. Absolute bioavailability was 89 ± 11%, total clearance was 1.44 ± 0.30 l/h, and intercompartment distribution was 2.3 ± 1.1 l/h; the volumes of distribution were 3.8 ± 0.8 l for the central compartment and 1.7 ± 0.6 l for the peripheral compartment. The mean absorption time increased from 7 h with the 45 mg dose to 10 h with the 180 mg dose, and the terminal half-life increased as well from 3.46 to 4.35 h (35).

Clinical Studies

The antiviral effects of enfuvirtide reported from *in vitro* and *in vivo* studies have been confirmed by clinical studies conducted in HIV-1 infected patients. In the

Table II: Median pharmacokinetic values after i.v. administration of a single dose or multiple doses (steady-state) of pentafuside (adapted from 32).

		3 mg	10 mg	30 mg	100 mg
Maximum observed concentration	Single dose	0.37 μg/ml	1.61 μg/ml	5.37 μg/ml	18.30 μg/ml
	Steady state	0.39 μg/ml	1.53 μg/ml	5.55 μg/ml	20.67 μg/ml
Maximum theoretical concentration	Single dose	0.45 μg/ml	1.97 μg/ml	6.25 μg/ml	21.23 μg/ml
	Steady state	0.43 μg/ml	1.81 μg/ml	6.82 μg/ml	24.10 μg/ml
Area under curve	Single dose	1.19 mg/h/ml	4.41 mg/h/ml	15.92 mg/h/ml	51.70 mg/h/ml
	Steady state	1.11 mg/h/ml	4.89 mg/h/ml	16.39 mg/h/ml	64.43 mg/h/ml
Trough concentration	Single dose	0.02 μg/ml	0.01 μg/ml	0.04 μg/ml	0.05 μg/ml
	Steady state	0.02 μg/ml	0.05 μg/ml	0.32 μg/ml	1.02 μg/ml
Volume of distribution	Single dose	6.71 l	5.08 l	4.81 l	4.71 l
	Steady state	7.01 l	5.66 l	4.40 l	4.15 l

TRI-001 study, twice-daily i.v. administration of enfuvirtide for 14 days to 16 subjects induced dose-dependent reductions in plasma viral RNA levels of up to 1.96 $\log_{10}$, and the viral elimination kinetics were similar to those described for highly active antiretroviral therapies (HAART) (32). The results of this study and some of the following studies are summarized in Table III.

A study conducted in 78 heavily pretreated patients with plasma HIV RNA values > 5000 copies/ml who received enfuvirtide doses of 12.5-200 mg/day by s.c. infusion or b.i.d. injection reported a dose-dependent reduction of plasma HIV RNA levels ranging from 0.3-1.6 $\log_{10}$ copies/ml (36). In children aged 3-12 years old, s.c. administration of enfuvirtide 60 mg/m^2 b.i.d. resulted in a 1.04 $\log_{10}$ decrease in plasma HIV RNA levels after 7 days of treatment, and virological suppression (defined as HIV RNA levels > 1 $\log_{10}$ below baseline levels) was maintained in most patients after 24 weeks of treatment (37). A crossover study confirmed the safety, tolerability and antiviral activity of the 100 mg/ml CO_3 formulation for twice-daily s.c. administration of enfuvirtide (38). Finally, flow cytometry studies revealed that enfuvirtide protects human CD4$^+$ lymphocytes from the cytotoxic effects of HIV-1 infection and results in a dose-dependent restoration of the CD4/CD8 ratio (28).

Some work has also been done on the combined administration of enfuvirtide and other antiviral drugs. A controlled phase II study assessed the safety and activity of three s.c. doses of enfuvirtide (50, 75 and 100 mg b.i.d.) combined with a fixed regimen of oral antivirals (abacavir 300 mg b.i.d., amprenavir 1200 mg b.i.d., ritonavir 200 mg b.i.d. and efavirenz 600 mg q.d.) in 71 adult patients previously treated with protease inhibitors but not non-nucleoside reverse transcriptase inhibitors. The addition of enfuvirtide to the therapeutic regimen increased the virological (decrease in plasma viral levels) and immunological (CD4$^+$ cell count) response of the oral antivirals after 48 weeks of treatment (39, 40).

Two other randomized phase III studies (TORO 1 and TORO 2) are currently being conducted in the U.S. and in Europe and Australia, respectively, to assess the safety and efficacy of enfuvirtide combined with oral antiretrovirals in treatment-experienced patients. Recently, 24-week results from the TORO 1 study were reported. In this study, administration of enfuvirtide combined with an individualized antiretroviral treatment produced a significant additional decrease in the amount of virus in the blood as compared to an individualized antiretroviral treatment alone. The incidence of grade 3 and 4 laboratory abnormalities, clinical adverse events and the percentage of drug discontinuations at 24 weeks was very similar for the enfuvirtide and control arms. Most patients in the enfuvirtide arm showed injection site reactions, but only 3% of patients discontinued the study as a consequence. Other adverse events that were more frequent in the enfuvirtide arm than in the control arm were insomnia, headache, peripheral neuropathy and dizziness, but no causal relationship could be established for enfuvirtide (41).

Positive 24-week results from the TORO 2 study have also been presented. The results show that enfuvirtide administered in combination with an optimized antiretroviral treatment regimen provides a significant additional decrease in the amount of virus in the blood as compared to an optimized antiretroviral treatment regimen alone. In total, 504 HIV-infected patients in Europe and Australia took part in TORO 2. They were treatment-experienced and/or had documented resistance to each of the three classes of currently available anti-HIV drugs. At baseline, patients had a median HIV RNA level of over 5 $\log_{10}$ copies/ml and extensive prior exposure to multiple anti-HIV drugs. At 24 weeks, patients receiving enfuvirtide as part of their regimen had a mean reduction in HIV levels of 1.43 $\log_{10}$ copies/ml compared to 0.65 $\log_{10}$ copies/ml for those in the control arm. The difference in the magnitude of decrease in HIV between the two arms at 24 weeks was 0.78 $\log_{10}$ copies/ml, which was statistically significant (42).

Enfuvirtide is also well tolerated. No patients were withdrawn from the TRI-001 study because of adverse events after i.v. administration of enfuvirtide for 14 days. Four subjects showed an increase in body temperature, but the two cases of temperatures higher than 38.6 °C were probably caused by other clinical events, such as community-acquired pharyngitis or phlebitis at the i.v. catheter. A possible relationship between enfuvirtide and isolated cases of mild to moderate headaches was sug-

Table III: Clinical studies of enfuvirtide in patients with HIV+ serology (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Open	Enfuvirtide, 3 mg iv over 20 min bid x 14 d (n=4) Enfuvirtide, 10 mg iv over 20 min bid x 14 d (n=4) Enfuvirtide, 30 mg iv over 20 min bid x 14 d (n=4) Enfuvirtide, 100 mg iv over 20 min bid x 14 d (n=4)	17	Short-term administration of enfuvirtide was safe and effective as a potent inhibitor of HIV replication in a dose-dependent manner in HIV-infected patients	32
Randomized, open, multicenter	Enfuvirtide, 12.5-200 mg sc bid + prior stable antiretroviral regimen x 28 d (n=78)	78	Enfuvirtide was a safe and potent antiretroviral agent	36
Multicenter	Enfuvirdine, 30 mg/m^2 (increased to 60 mg/m^2 if needed) sc bid + prior stable antiretroviral regimen (n=4) Enfuvirdine, 60 mg/m^2 sc bid + prior stable antiretroviral regimen (n=10)	14	Enfuvirtide was well tolerated and caused a rapid and potent suppression of HIV RNA when added to antiretroviral therapy in children with HIV-1 infection	37
Crossover	Enfuvirtide (100 mg/ml CO_3 formulation), 75 mg sc bid + prior antiretroviral regimen x 48 wk (n=12) Enfuvirtide (50 mg/ml CO_3 formulation), 100 mg sc bid + prior antiretroviral regimen x 48 wk (n=22) Enfuvirtide (100 mg/ml TRIS formulation), 100 mg sc bid + prior antiretroviral regimen x 48 wk (n=12)	46	Enfuvirtide CO_3 and Tris formulations had similar safety profiles, but the enfuvirtide 100 mg/ml CO_3 formulation showed a greater activity. Injection site reactions were the most frequent adverse events but did not cause any withdrawals	38
Randomized, open	Enfuvirtide, 50 mg sc bid + Abacavir, 300 mg po bid + Amprenavir, 1200 mg po bid + Ritonavir, 200 mg po bid + Efavirenz, 600 mg po od x 48 wk (n=16) Enfuvirtide, 75 mg sc bid + Abacavir, 300 mg po bid + Amprenavir, 1200 mg po bid + Ritonavir, 200 mg po bid + Efavirenz, 600 mg po od x 48 wk (n=20) Enfuvirtide, 100 mg sc bid + Abacavir, 300 mg po bid + Amprenavir, 1200 mg po bid + Ritonavir, 200 mg po bid + Efavirenz, 600 mg po od x 48 wk (n=16) Abacavir, 300 mg po bid + Amprenavir, 1200 mg po bid + Ritonavir, 200 mg po bid + Efavirenz, 600 mg po od x 48 wk (n=19)	71	Enfuvirtide added to a standard antiretroviral regimen was well tolerated and achieved an improved virologic and immunologic response in NNRTI-naive patients with HIV-1 infection failing protease inhibitor therapy	39, 40
Open	Enfuvirtide, 50 mg sc bid + prior stable antiretroviral regimen x 48 wk (n=70)	70	Twice-daily subcutaneous enfuvirtide injections did not appear to limit activities of daily living	42

gested. Finally, no chemical or hematological alterations were found in patients during this study (32). Other studies reported mild to moderate cases of induration and erythema at the site of s.c. administration of enfuvirtide, but no treatment-related severe systemic toxicities were observed (36, 39, 40). Subcutaneous administration of enfuvirtide is especially attractive, since the degree of satisfaction of the patients is good and does not affect their daily living activities (43). Subcutaneous or intravenous administration of enfuvirtide may result in the development of antibodies reactive against the drug; however, these antibodies do not alter the drug's efficacy, pharmacokinetic parameters or good safety profile (44). Studies conducted on children aged 3-12 years old have also reported a good safety profile of enfuvirtide in pediatric patients (37).

Conclusions

Enfuvirtide is the leading member of a new family of antiviral drugs that inhibit HIV-1 replication by blocking virus entry into the host cell. It is an effective drug that reduces plasma viral loads and increases the immunological status of HIV-1 infected patients. Enfuvirtide also has a good safety profile; no systemic toxicological reactions have been described and the most common adverse events related to treatment consist of mild to moderate injection site reactions. The drug is equally suitable for treating adult and pediatric patients.

The most important feature of enfuvirtide is its novel mechanism of action, which allows combination with protease inhibitors and/or reverse transcriptase inhibitors. The simultaneous administration of antiretroviral drugs that interfere with different stages of the viral life cycle may lead to a more effective inhibition of HIV-1 replication, while decreasing the emergence of drug-resistant virus and thereby preserving a patient's therapeutic options. This could also result in the administration of lower doses of each drug included in a specific therapeutic combination, which would likely result in less toxicity than with single drug therapies. These combinations are currently being assessed in several phase III clinical stud-

ies with oral antiretrovirals and enfuvirtide in treatment-experienced patients.

Source

Discovered by Duke University, Durham, NC (US) and Trimeris, Inc. (US); licensed to F. Hoffman-La Roche AG (CH).

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