Enfuvirtide, a New Treatment for HIV Infection

Summary

✓ Enfuvirtide is the first in a new class of drugs called fusion inhibitors. It was recently approved in Canada for the treatment of patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Current evidence on safety and efficacy is limited to 48-week studies.

✓ Two phase III trials found that in treatment-experienced patients failing antiretroviral treatment, the addition of subcutaneous enfuvirtide to an optimized oral background antiretroviral regimen significantly reduced viral load and increased CD4 cell counts.

✓ Potential high cost and limited supply may reduce access to this treatment.

The Technology

Enfuvirtide (also called pentafuside or T-20) is the first in a new class of drugs, known as fusion or entry inhibitors, to be used in the treatment of patients with human immunodeficiency virus (HIV). HIV causes immunodeficiency mainly by decreasing the number of CD4 lymphocytes. Unlike antiretroviral agents that act intracellularly, enfuvirtide binds to HIV and prevents its attachment to the CD4 cell, thus stopping viral entry into host cells and preventing the fusion of viral and cellular membranes.

Despite advances in HIV management, many patients experience virologic failure. The development of resistance to one antiretroviral agent often confers resistance to others in the same drug class. Likely because of its unique mechanism of action, viral isolates that are resistant to other antiretroviral agents have not demonstrated cross-resistance to enfuvirtide. Mutations associated with decreased susceptibility to enfuvirtide, however, have been documented.

Regulatory Status

Enfuvirtide (Fuzeon™, Hoffmann-La Roche Ltd.) was approved in Canada on July 14, 2003. In combination with other antiretroviral agents, enfuvirtide is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing retroviral therapy. It is, however, still unavailable in Canada. It was also approved in the US (March 2003) and Europe (May 2003) for a similar indication.

Patient Group

HIV infection, which is transmitted via parenteral, perinatal and sexual contact, is characterized by the body’s inability to maintain immunocompetence. Men who have sex with men and intravenous drug users represent the majority of the approximately 55,000 Canadians living with HIV as of 2001.
HIV-1 is the most prevalent cause of acquired immunodeficiency syndrome (AIDS), while HIV-2, which may be less pathogenic, is less common. The median time from the initial HIV infection for an untreated person to develop AIDS is approximately 10 years.2

Current Practice

Antiretroviral therapy has a profound impact on disease progression and survival.2 Highly active antiretroviral therapy (HAART) is the current standard.2 Multiple antiretroviral drugs are combined to maximize effectiveness. One of the following recommended regimens is used: one non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs); one or two protease inhibitors (PIs) plus two NRTIs; or three NRTIs.12 New agents demonstrate antiretroviral activity even in treatment-experienced patients with multidrug resistance.12 Adding one active agent to a failing regimen, however, may lead to drug resistance.12 Additional drugs may be required to treat or prevent HIV-associated conditions. The resulting drug combinations increase the potential for adverse effects and poor patient compliance, leading to resistance and treatment failure.12

The Evidence

Two phase III randomized, open-label, controlled, parallel-group trials have been completed: the T-20 versus Optimized Regimen Only Study 1 and 2 (TORO 1 and TORO 2).13,14 Detailed data are available for the first 24 weeks of the 48-week trials (Table 1).

Both trials have a similar design with the exception of patients’ previous therapies. The effect of enfuvirtide (90 mg subcutaneously twice daily) plus optimized background (OB) therapy is compared to that of OB, which consists of a combination of three to five antiretroviral agents based on a patient’s treatment history. Patients enrolled in TORO 1

Table 1: Summary of results at 24 weeks

<table>
<thead>
<tr>
<th>Study Parameters</th>
<th>TORO 1</th>
<th>TORO 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enf + OB</td>
<td>OB</td>
</tr>
<tr>
<td>Number of patients</td>
<td>326</td>
<td>165</td>
</tr>
<tr>
<td>Decrease from baseline to week 24 [HIV-RNA (log_{10} copies/mL)]</td>
<td>1.70^a</td>
<td>0.76</td>
</tr>
<tr>
<td>Increase from baseline to week 24 [CD4 counts (cells/mm^3)]</td>
<td>76^a</td>
<td>32</td>
</tr>
<tr>
<td>% Patients with &lt;50 copies/mL HIV-RNA</td>
<td>19.6^a</td>
<td>7.3</td>
</tr>
</tbody>
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^a p<0.001, ^b p=0.02, ^c p=0.01, Enf=enfuvirtide
The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments. (www.ccohta.ca)

Previously received at least six months of treatment, including exposure to one NRTI, one NNRTI and two PIs; documented resistance to these drugs; or both. In TORO 2, patients were required to have had treatment for at least three months with exposure to each drug class, demonstrated resistance to each class or both. The treatment regimens were determined before the 2:1 randomization schedule.

The primary efficacy endpoint was the change in HIV-RNA level from baseline to week 24. Secondary endpoints included changes in CD4 cell counts. Changes to the treatment regimen were permitted for the management of toxic effects or for virologic failure. Subjects who exhibited treatment failure at eight weeks were encouraged to change their OB regimen; control-group subjects were permitted to add enfuvirtide.

The preliminary 48-week results from the TORO 1 and 2 trials were recently presented (Table 2). The effect of enfuvirtide seems to be sustained through the first year of use.

<table>
<thead>
<tr>
<th>Study Parameters</th>
<th>Enf + OB</th>
<th>OB</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>661</td>
<td>334</td>
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<tr>
<td>Decrease from baseline to week 48 [HIV-RNA (log10 copies/mL)]</td>
<td>1.48a</td>
<td>0.63</td>
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<tr>
<td>Increase from baseline to week 48 [CD4 counts (cells/mm^3)]</td>
<td>91a</td>
<td>45</td>
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<td>% Patients with &lt;50 copies/mL HIV-RNA</td>
<td>18.3a</td>
<td>7.8</td>
</tr>
</tbody>
</table>

a p<0.0001

Published data on enfuvirtide use in children is limited to one open-label, uncontrolled phase I-II study involving 14 children aged four to 12 years. At 24 weeks, three subjects (21%) achieved a HIV-RNA level of <50 copies/mL. A median increase from baseline in the CD4 T cell counts of 146/mm^3 (95% CI: 13, 655) was observed in 11 subjects.

Adverse Effects

An increased rate of pneumonia, primarily bacterial, was observed in the enfuvirtide group compared with the control group, in the combined safety analysis of TORO 1 and 2, both at 24 weeks (4.9 versus 0.6 per 100 patient-years) and 48 weeks (6.6 versus 0.6 per 100 patient-years). Bacterial pneumonia was included as a precaution in the product monograph. A trend towards (p=0.37) a higher rate of sepsis was observed in the combined enfuvirtide group. Two cases of systemic hypersensitivity to enfuvirtide, which persisted on re-challenge, were also reported.

Almost all patients (98.2%) had at least one injection site reaction (ISR), mostly mild or moderate. Less than 10% of the patients in each trial had a more serious ISR, resulting in the use of analgesics, hospitalization or limits on daily activities. ISR-related infection
occurred in 1% of subjects. It is estimated that 2.5% of subjects discontinued treatment because of ISRs at 24 weeks (4.4% at 48 weeks). ISRs were also observed in children.

**Administration and Cost**

Enfuvirtide, which is available as a single-use vial, must be reconstituted before subcutaneous injection. Recommended doses are 90 mg twice daily for adults and 2 mg/kg twice daily for children (six to 16 years). In the US, the wholesale cost for a one-year supply is approximately US$20,000. The Canadian price has not yet been released.

**Concurrent Developments**

New drug classes being tested include nucleotide analogues, immunomodulation agents, vaccines and drugs targeting viral entry. The latter class include the fusion inhibitor T-1249, chemokine co-receptor antagonists and attachment inhibitors.

**Rate of Technology Diffusion**

Because of a complex manufacturing process, there may only be enough enfuvirtide over the next year to supply approximately 15,000 patients worldwide, mainly in industrialized nations. Expected high acquisition costs may limit its use.

Patients’ acceptance of self-injection was studied in phase II and phase III trials, using the Subcutaneous Injection Survey. Self-injection was not a barrier to the use of enfuvirtide in the populations studied. The needle of the enfuvirtide syringe automatically retracts into the syringe after use. While this reduces the risk of needlestick injuries, the disposal of HIV-infected needles will require special arrangements.

**Implementation Issues**

The addition of enfuvirtide to a failing antiretroviral regimen sustains the clinical response over one year. Long-term efficacy and safety studies are required to determine enfuvirtide’s place in therapy. The current recommendation is to limit its use to heavily treatment-experienced patients. An open-label phase III study is underway to assess serious adverse events.

**References**


21. Green J, Wintfeld N. Patient acceptance with self-injection of enfuvirtide (T-20) for HIV over 24 weeks of treatment [abstract]. Sixth International Congress on Drug Therapy in HIV Infection; 2002; Glasgow, UK.