Clinical perspective of fusion inhibitors for treatment of HIV

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The number of antiretroviral-experienced HIV patients with multiple resistances against the currently available antiretroviral drug classes is increasing substantially. Therapeutic options for this specific group of patients are limited. The fusion inhibitor enfuvirtide represents the first new therapeutic option from a new drug class for this patient population. An optimized background therapy with remaining antiviral activity appears essential in order to avoid resistance development against enfuvirtide. Despite the high price of enfuvirtide, cost-effectiveness and increase in quality of life have been demonstrated in patients achieving virological control under optimized background and enfuvirtide therapy. In this article, the characteristics and clinical perspectives of fusion inhibitors are presented and discussed.

Keywords: antiretroviral therapy, enfuvirtide, HAART, salvage therapy

Introduction

With the introduction of highly active antiretroviral therapy (HAART) a substantial reduction in HIV-associated morbidity and mortality can be achieved.[1] Long-term treatment success rates, however, are limited by a variety of factors including compliance issues, short- and long-term toxicity of antiretroviral agents, unfavourable pharmacokinetic profiles and differences in potency. As a result, in clinical practice virological failure rates of up to 50% are common within the first 2 years after initiation of HAART.[2] As a consequence of ongoing viral replication, resistance emerges and currently more than 50% of HIV-infected patients receiving antiviral therapy have developed resistance to at least one of the compounds of their current regimen.[3] Therefore the development of new agents from new drug classes without cross-resistance to currently available substances is urgently needed to initiate successful treatment strategies in pre-treated patients with virological failure as a result of antiretroviral resistance development. With the introduction of T-20 (enfuvirtide, Fuzeon) as the first compound from the new drug class of fusion inhibitors, a promising new treatment option has become available in heavily pre-treated patients. In order to maximize the benefit from the new treatment opportunities, however, it appears advisable to develop specific treatment guidelines for the use of fusion inhibitors in different patient settings. This article aims to highlight clinical strategies for the use of new fusion inhibitors and to define the use of T-20 in different treatment situations.

General issues in changing antiretroviral therapy

The main reasons to change antiretroviral therapy are virological failure or toxicity. Virological failure is characterized by persistent detectable plasma viral load in the presence of antiretroviral therapy. The reasons for virological failure are multi-factorial and may include problems of adherence, drug–drug interactions, pharmacokinetic issues and the occurrence of resistance. In the presence of persistent viral replication under therapy, the accumulation of key resistance mutations over time will increase the level of resistance as well as the risk of cross-resistance within each class of drugs.

In the case of virological failure, a detailed history of current or past antiretroviral medication as well as other HIV-related medications is necessary. Testing for antiretroviral drug resistance may be very helpful in maximizing the number of active drugs. Resistance testing is therefore recommended in all patients failing under therapy (see European guidelines on resistance[4]). In order to develop guidelines in this more complex treatment situation, different failure situations have recently been defined (Table 1).[5]

In patients with virological failure, further work-up should consist of an adherence assessment and if necessary discussion of ways to improve adherence, the exclusion of potential drug–drug or drug–food interactions and also the exclusion of an intercurrent infection or recent vaccination as a reason for a temporary increase in HIV-RNA. A pharmacokinetic assessment of drug levels may give additional guidance. In case of a confirmed virological failure in a further viral load determination a few weeks later, and after performance of resistance testing, a possible switch or intensification of antiviral therapy needs to be addressed.

In the case of drug toxicity without virological failure, it is appropriate to substitute one or more drugs from the class of agents suspected to be the cause of drug toxicity.

Antiretroviral treatment after virological failure

For the defined situations in stages 1–3b (Table 1), presumably enough active 'traditional' compounds remain after resistance testing

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Table 1. Virological failure: a classification according to Staszewski[5]

Stage 1:	patients failing virologically (HIV-RNA > 500 copies/mL) but without development of resistance
Stage 2a:	patients failing virologically on the first regimen and developing resistance
Stage 2b:	patients remaining on the failing first regimen and accumulating further resistance
Stage 3a:	patients failing virologically (moderate resistance but still remaining options) but still showing immunological response
Stage 3b:	patients failing virologically (moderate resistance but still remaining options) and failing immunologically
Stage 4a:	patients showing significant multiclass resistance, failing virologically but still showing a persistent immunological benefit
Stage 4b:	patients showing significant multiclass resistance and failing virologically and immunologically

for the composition of a new therapy. In general, three active compounds are required to gain a high likelihood of achieving virological control. The introduction of an agent from a new drug class with different resistance features has been independently shown to be associated with a higher subsequent virological treatment success rate than the cycling or use of new drugs from previously already failed drug classes.[6] In patients with more advanced stages of pre-treatment and fewer remaining active options (stages 4a and 4b), the use of fusion inhibitors as a new drug class lacking cross-resistance appears to be especially attractive.

The first component of this class is enfuvirtide, formerly called T-20. It is a novel 36-amino-acid synthetic peptide that binds to the HR-1 region of HIV-1 GP41 and inhibits the fusion of the virus with CD4 cells. Two open-label randomized Phase III controlled trials (TORO 1 and 2) demonstrated that enfuvirtide added to an optimized background of antiretrovirals on the basis of genotypic and phenotypic resistance testing significantly improves virological response, increases the time to virological failure and increases CD4 cell count compared with optimized background alone.[7,8] Most recently, the data on further follow-up of 48 weeks was presented confirming the antiviral activity of enfuvirtide to be maintained throughout 48 weeks.[9] Indeed, at 48 weeks, patients receiving enfuvirtide as part of the individualized regimen, achieved a mean reduction in HIV-RNA levels of $1.48 \log_{10}$ copies/mL compared with a mean reduction of $0.63 \log_{10}$ copies/mL for those randomized to the individualized background regimen without the option of adding a fusion inhibitor. The difference in the scale of decrease in HIV-RNA between the two arms at 48 weeks was $0.85 \log_{10}$ copies/mL. The change from baseline for CD4 cell count was an increase of 91 cells/mm^3 for the fusion inhibitor-containing arm versus 45 cells/mm^3 for the control arm on optimized background only. The percentage of patients achieving reduction in HIV-1 viral load to undetectable levels (<400 copies/mL) was 30.4% for the T-20-containing arm versus 12% for the control arm. All of these differences were statistically significant ($P < 0.0001$). In further subanalysis, it became clear that various factors predict a response to fusion inhibitor therapy. The greatest benefit associated with enfuvirtide was observed in patients with a higher CD4 cell count at baseline (≥100 cells/mm^3), a viral load <100 000 copies/mL, less than 10 prior antiretrovirals, and at least two or more active antiretrovirals in the

optimized background therapy chosen from resistance testing.[10] Sex, ethnicity and age did not affect response to enfuvirtide. The ability of participants to assemble a background regimen that contained active drugs was pivotal. People who were sensitive to just one of the drugs in addition to T-20 achieved a drop in viral load of 0.2 log after 24 weeks, those with sensitivity to three or four background drugs achieved a 1.23 log drop in comparison. In addition, a better response was seen in those patients who had the boosted protease inhibitor lopinavir/ritonavir included in their background regimen whilst those patients with prior experience of this drug responded more poorly than those without. From these results, it can be concluded that patients in stages 3a and 3b may benefit most from treatment with enfuvirtide in conjunction with resistance testing as a guidance for choosing the additional antiretrovirals.

Considering the high price of T-20, great interest has been raised around cost-effectiveness analysis. Recently, data were presented showing that when enfuvirtide was used as part of an optimized background regimen, it was a cost-effective treatment for HIV patients with a cost per quality-adjusted life-year (QALY) gained of approximately £23 000 when compared with conventional optimized background therapy.[11] Cost-effectiveness could be increased further by using enfuvirtide in patients with higher CD4 cell levels and more active agents in the background therapy. Interestingly, further subanalysis examining the impact of enfuvirtide on health-related quality of life (HRQoL) at 48 weeks demonstrated an improvement in HRQoL when enfuvirtide was added to background regimens and self-administered for 48 weeks by treatment-experienced HIV-1-infected individuals.[12] Improvement in quality of life was found to correlate with virological response. These findings are important as they occurred even though this was a subcutaneous injection therapy, clearly showing that the overall improvement in the setting of virological control even overcomes more complicated ways of administration of antiviral therapy.

Resistance to fusion inhibitors

In patients where enfuvirtide was added to a failing regimen, development of resistance was common and noted within several weeks of treatment.[13] This indicates that functional monotherapy with enfuvirtide has a limited impact because of the development of resistance and additional active drugs are needed to preserve the antiviral efficacy. Interestingly, T-1249, another fusion inhibitor in development, does not exhibit cross-resistance to T-20-resistant HIV strains and may be an option for sequential or combined treatment strategies.

Adverse events

The prevailing adverse event in treatment with enfuvirtide is the development of painful subcutaneous nodules at the injection site. The histological examination of the nodules showed an eosinophilic reaction suggesting a localized hypersensitivity reaction. No successful management strategies to prevent this local reaction are available to date. However, achieving and maintaining good subcutaneous injection technique may be the most significant means of managing injection-site reactions. The use of enfuvirtide may also be associated with an increased incidence of bacterial pneumonia but more data are needed to define more clearly the significance of this finding. No other specific adverse events have been observed so far.

Clinical perspective of fusion inhibitors

Taking into account the results from the TORO trials, overall two main settings can be defined in which the clinical use of T-20 can be recommended. The first setting is patients who according to the virological failure classification are in the last stage (4b), who show significant resistance to all antivirals from the three previously available drug classes for treatment of HIV and have failed virologically and immunologically. In these patients, although the benefit from T-20 may be the least, there are hardly any other options left and with the use of a new drug class, at least a partial and temporary immune response may lead to an overall clinical benefit, i.e. delay of disease progression and overall increased survival. If possible, T-20 should be combined in ongoing clinical trials in these patients with other agents that may offer some activity in multi-resistant virus strains such as tipranavir or TMC-114. In patients in earlier stages of virological failure with moderate to significant resistance but with ≥2 but ≤3 active substances remaining according to resistance analysis, T-20 would be an option as a combination partner together with two other active substances (stages 3a and 3b).

References

1. Palella, F. J., Deloria-Knoll, M., Chmiel, J. S. *et al.* (2003). Survival benefits of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Annals of Internal Medicine* **138**, 620–6.

2. Fatkenheuer, G., Theisen, A., Rockstroh, J. *et al.* (1997). Virological treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients. *AIDS* **11**, F113–F116.

3. Richman, D. D., Bozette, S., Morton, S. *et al.* (2001). The prevalence of antiretroviral drug resistance in the US. *Presented at the Forty-First Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 2001.* Abstract LB-17. American Society for Microbiology, Washington, DC, USA.

4. The EuroGuidelines Group for HIV Resistance. (2001). Clinical and laboratory guidelines for the use of HIV-1 drug resistance testing as part of treatment management: recommendations for the European setting. *AIDS* **15**, 309–20.

5. Staszewski, S. (2003). Novel strategies for salvage therapy. In *Program of the Second International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment, Paris, 2003.* Abstract 114, p. 73. IAS International AIDS Society, Stockholm, Sweden.

6. Hammer, S. M., Vaida, F., Bennett, K. K. *et al.* (2002). Dual vs single protease inhibitor therapy following antiretroviral treatment failure: a randomized trial. *Journal of the American Medical Association* **288**, 169–80.

7. Lalezarei, J., Henry, K., O'Hearn, M. *et al.* (2003). Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *New England Journal of Medicine* **348**, 2175–85.

8. Lazzarin, A., Clotet, B., Cooper, D. *et al.* (2003). Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *New England Journal of Medicine* **348**, 2186–95.

9. Katlama, C., Arasteh, K., Clotet, B. *et al.* (2003). Enfuvirtide TORO studies: 48 week results confirmed 24 week findings. In *Program of the Second International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment, Paris, 2003.* Abstract LB2, p. 280. IAS International AIDS Society, Stockholm, Sweden.

10. Montaner, J., DeMasi, R., Delehanty, J. *et al.* (2003). Analysis of virological response of enfuvirtide in TORO. Implications for patient management. In *Abstracts of the Second International AIDS Society Conference on HIV Pathogenesis and Treatment, Paris, 2003.* Abstract 116. *Antiviral Therapy* **8**, Suppl. 1, S212.

11. Hornberger, J., Youle, M., Beck, E. J. *et al.* (2003). Cost-effectiveness of enfuvirtide from UK health payer perspective. In *Abstracts of the Ninth European AIDS Conference, Warsaw, 2003.* Abstract 19.5/1. European AIDS Clinical Society, Paris, France.

12. Clumeck, N., Cohen, C. J., Thompson, M. *et al.* (2003). Impact of enfuvirtide on health-related quality of life at 48 weeks. In *Abstracts of the Ninth European AIDS Conference, Warsaw, 2003.* Abstract 7.3/19. European AIDS Clinical Society, Paris, France.

13. Wei, X., Decker, J. M., Liu, H. *et al.* (2002). Emergence of resistant human immunodeficiency virus type 1 in patients receiving fusion inhibitor (T-20) monotherapy. *Antimicrobial Agents and Chemotherapy* **46**, 1896–905.