Drugs 2003; 63 (24): 2767-2768
0012-6667/03/0024-2767/$33.00/0

Enfuvirtide
A Viewpoint by Jacob Lalezari

Mount Zion Hospital/UCSF, Quest Clinical Research, San Francisco, California, USA

Enfuvirtide (Fuzeon™, T20, DP178), the first fusion inhibitor approved for the treatment of HIV, inhibits glycoprotein (gp)41-mediated fusion of HIV to host CD4+ cells, thereby blocking viral entry. This unique extracellular mechanism of action appears to explain enfuvirtide's preserved activity against viral mutants that are resistant to other classes of antiretroviral therapy. Exciting results from two international phase III studies, conducted in patients with virological failure and documented resistance to all three classes of antiretroviral drugs (i.e. patients requiring 'salvage' therapy), confirm the benefit of enfuvirtide administered twice daily as 90mg subcutaneous injections, thereby providing real hope for patients with progressive HIV disease and limited treatment options.

Although a welcome addition to the HIV armamentarium, questions concerning the appropriate use of enfuvirtide remain. Foremost among these is the question of when to start treatment. The phase III studies showed the substantial benefit of enfuvirtide across all patient subgroups, including patients with few or even no remaining treatment options. However, benefit was greatest and most durable when patients were able to combine enfuvirtide with other active agents. How should these results translate into appropriate priorities for the use of enfuvirtide?

At one end of the HIV spectrum, we have patients with early disease, relatively intact immune systems and multiple antiretroviral options who should save enfuvirtide for later as needed. Aside from considerations of cost (about $US20 000/year) and availability (which may be limited for some time), the need for twice-daily subcutaneous injections and high frequency of injection-site reactions (>90%, though most are mild to moderate) requires a significant commitment from patients to remain adherent, and that commitment is likely to be absent in patients who perceive their health as relatively stable.

In contrast, patients with failing health and no obvious treatment options should, in my view, be given priority access to enfuvirtide. Although antiviral effect in these patients may be transient due to the emergence of resistant virus, efforts should be directed at optimising background antivirals and providing patients at least a temporary reduction in viral load that often results in improved immune function and overall health. The question of whether to then continue enfuvirtide as part of a failing regimen has not been answered and should be based on overall clinical response with an eye to whether viral rebound returns to baseline levels. Indeed, one important finding from the phase III studies is that when patients do fail on enfuvirtide, they often maintain a 1-log decrease in viral load suggestive of impaired viral fitness that can be critical in the 'deep salvage' situation.

What about patients in the middle of the spectrum? For them, the optimal time to start enfuvirtide must be individualised and based on a number of factors including: (i) overall stability of the patient's health and T-cell count; (ii) patient readiness and motivation to commit to the twice-daily subcutaneous injections; (iii) availability of other agents to help optimise the background regimen; and (iv) possible tradeoffs from waiting for the emergence of new agents which can be combined with enfuvirtide later to derive a greater and more durable response.

In summary, enfuvirtide should be provided to patients in immediate need and then carefully targeted to motivated, 'early salvage' patients, i.e. before resistance and cross-resistance have become so deeply rooted that devising an effective background regimen becomes prohibitive. ▲