Summary

The HIV protease (or proteinase) enzyme is an essential component of the replicative cycle of HIV, performing the post-transitional processing of the gag and gag-pol gene products into the functional core proteins and viral enzymes. Inhibition of this enzyme leads to production of immature noninfectious viral progeny, and hence prevention of further rounds of infection. Structurally, the enzyme is a homodimer consisting of two identical 99 amino acid chains. HIV protease is a member of the aspartic protease family but is structurally dissimilar to human aspartic proteases such as renin, gastricsin and cathepsin D and E, suggesting the possibility of creating inhibitors with a wide therapeutic index.

At least 6 inhibitors of HIV protease are currently in clinical development: saquinavir, indinavir, ritonavir, nelfinavir (AG-1343), KNI-272 and VX-478, the first four of which have shown antiretroviral activity and acceptable tolerability in initial phase III clinical trials.

Resistance or reduced sensitivity to the leading protease inhibitors has been reported in vivo and appears to be associated with loss of therapeutic effect. However, resistance patterns appear to be distinct. Treatment for 1 year with indinavir has been reported to lead to selection of virus in 4 patients, which was cross-resistant to all other leading protease inhibitors. On the other hand, a larger series of clinical isolates from patients receiving saquinavir alone or in combination with zidovudine for up to 3 years did not lead to virus cross-resistant to either indinavir or ritonavir. This suggests that care should be exercised in designing the sequence of protease usage. Additionally, differing resistance patterns may be used to select combinations of protease inhibitors in future trials.

Data from studies combining protease inhibitors with nucleoside analogues suggest value in terms of larger and more prolonged virological and immunological marker responses than are observed with single agent therapy, and this is likely to be the primary role for protease inhibitors; both in initial combinations for patients commencing therapy and as add-in therapies for patients previously treated with antiretrovirals. However, in vitro and animal pharmacokinetic studies also give evidence of the possibility of combining protease inhibitors, potentially leading to improved bioavailability, antiviral synergy and delay in emergence of viral resistance.
Current therapy for HIV infection involves combination or monotherapy with the available nucleoside analogue reverse transcriptase inhibitors, zidovudine, zalcitabine, didanosine and stavudine. A fifth member of this class, lamivudine, has recently been licensed in the US. Despite providing modest improvements in survival and delaying clinical disease progression, therapy with these agents invariably fails, at least in part due to the selection of viral variants with reduced susceptibility.

Prolonged use of nucleoside analogues is further limited by a range of clinical and laboratory toxicities frequently related to interference with human cellular metabolism at the level of mitochondrial DNA polymerase-γ.[6,7] Sequential use of some nucleoside analogues may be limited by viral or cellular cross-resistance[5,8,9] and overlapping toxicity patterns.[10] Additionally, as these agents require intracellular triphosphorylation to their active form, competition between agents from the same nucleotide base, such as zidovudine and stavudine, or zalcitabine and lamivudine, may lead to reductions in nucleoside triphosphate levels[11] and hence clinical activity.[12]

Therefore, there exists an urgent need for new antiretroviral agents with both greater and more prolonged activity, and better long term tolerability which can more potently control viral replication, delay the emergence of resistance and, ultimately, improve clinical outcome.

This article describes a new class of antiretroviral agents, the HIV-protease (or proteinase) inhibitors, their rationale and mode of action, examines the in vitro and in vivo activity of the lead compounds and addresses the issue of viral resistance to this drug class.

1. Rationale for Protease Enzyme Inhibition

HIV aspartic protease is one of 4 virus-encoded enzymes which are potential therapy targets. This enzyme is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes (fig. 1).[13,14] Inhibition of the HIV protease leads to release of immature viral particles which are noninfectious.[15]

The HIV protease is structurally a symmetric homodimer derived from two identical 99 amino acid units.

Fig. 1. Production of the structural proteins and enzymes of HIV virions. Viral RNA is initially translated into gag or gag-pol polyprotein. The viral protease then begins the cascade of protein processing by cleaving itself out of the gag-pol polyprotein, before being free to process the remainder of the gag and gag-pol polyproteins into the fully functional proteins shown here. Envelope (env) protein precursor is cleaved by a cellular mechanism into the viral membrane proteins (gp120 and gp41). Abbreviations: IN = integrase; RNaseH = ribonuclease H; RT = reverse transcriptase.