ABSTRACT

Tremendous strides were made in reducing the morbidity and mortality associated with HIV infection with the introduction of protease inhibitor (PI) therapy. However, limitations in the tolerability and potency of initial PIs quickly emerged. The development of newer agents in this class attempts to address these concerns, offering less frequent dosing, lower pill burdens, and increased potency through pharmacokinetic boosting. This article considers how newer PIs that have been recently approved or are in late- or early-stage clinical development are meeting the challenge of effective potency. With improvements in efficacy and tolerability seen in clinical trials with these agents, newer PIs may offer opportunities for achieving suppression of viral replication while providing patients with greater flexibility and less impact on their daily lives. (Adv Stud Med. 2003;3(10B):S975-S980)

PROCEEDINGS

CLINICAL EXPECTATIONS OF EFFICACY: PROTEASE INHIBITOR POTENCY*

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*Based on a presentation given by Dr Young at a symposium held in conjunction with the 2nd IAS Conference on HIV Pathogenesis and Treatment.
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WHAT DEFINES POTENCY?

Potency is an aggregate of multiple factors. These include the inherent potency of the drug—its antiviral effect—and clinical effectiveness, or how well a patient responds in the context of his or her overall treatment strategies. Long-term potency must include a consideration of side effects, which can create a barrier to realizing the potential of an agent. As “inherent potency” of the class is continually refined, short-term side effects may be emerging as especially important considerations for newer agents. New PIs address some of the problems of potency seen with older agents, and this article summarizes the clinical efficacy to date of 4 newer PI agents—atazanavir, fosamprenavir (“908”), tipranavir, and TMC-114.


**ATAZANAVIR**

This newly approved (June 2003) azapeptide inhibitor of HIV-1 protease is dosed as 400 mg once daily, and all clinical studies of atazanavir consistently demonstrate its favorable lipid side-effect profile. Specifically regarding the potency of atazanavir, final results of one phase 3 study, A1424-034, in ART-naive patients showed noninferiority of atazanavir versus efavirenz for the proportion of subjects achieving viral loads of less than 400 copies/mL at 48 weeks. However, only 32% and 37%, respectively, achieved a viral load of less than 50 copies/mL—significantly lower than the percentage in this category in

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**Table. Key Efficacy Trials to Date Evaluating New PIs**

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<td>ART naive</td>
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<td>48 weeks &lt;400 copies/mL: 70% ATV, 64% EFV; &lt;50 copies/mL: 32% ATV, 37% EFV</td>
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<td>A1424-043</td>
<td>ART experienced</td>
<td>ATV 400 mg qd vs LPV/r 400 mg/100 mg bid</td>
<td>24 weeks Median log change from baseline viral load: -1.76 ATV, -2.21 LPV/r</td>
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<td>ATV/r 300 mg/100 mg + TDF/N RTI vs ATV/SQV 400 mg/1200 mg + TDF/N RTI vs LPV/r + TDF/N RTI</td>
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*Updated 24-week data were presented subsequent to this symposium; see Badaro et al.*

PI = protease inhibitor; ART = antiretroviral therapy; ATV = atazanavir; 3TC = lamivudine; ZDV = zidovudine; EFV = efavirenz; LPV = lopinavir; r = ritonavir; TDF = tenofovir disoproxil fumarate; N RTI = nucleoside reverse transcriptase inhibitor; SQ V = saquinavir; 908 = fosamprenavir; ABC = abacavir; N FV = nelfinavir; TPV = tipranavir.
prior studies of efavirenz. Several reasons have been put forth to explain this relatively poor performance in both arms, and such controversy may be cause in itself to question the strength of the entire study.

For treatment-experienced patients, both unboosted and boosted atazanavir are being evaluated with lopinavir/ritonavir as the comparator (Table). Interim 24-week results from study AI424-043 showed that unboosted atazanavir (400 mg once daily) has efficacy inferior to standard-dose lopinavir/ritonavir in treatment-experienced patients. More people in study 043 dropped out due to virologic failure with atazanavir (3%) compared with lopinavir/ritonavir (0%). A more complex study, AI424-045, is evaluating 2 once-daily boosted-atazanavir regimens versus twice-daily lopinavir/ritonavir: atazanavir (300 mg) plus ritonavir (100 mg) once daily or atazanavir (400 mg) plus saquinavir (1200 mg) once daily. All PI-containing arms were in combination with tenofovir plus an NRTI. Interim 16-week results showed that the ritonavir-boosted atazanavir arm performed essentially as well as lopinavir/ritonavir; saquinavir-boosted atazanavir performed substantially more poorly than both of the other arms. Updated 24-week data have confirmed these general findings.

Considerations of potential clinical importance include the following: whether atazanavir should always be given with ritonavir, although studies of boosted atazanavir in ART-naive patients have not been done; and the effects of tenofovir and efavirenz in lowering plasma levels, and thus exposure, of atazanavir. This latter fact again raises the need for boosting of atazanavir with ritonavir in patients also taking tenofovir or efavirenz.

**Fosamprenavir (“908”)**

Fosamprenavir (“908”) is the newly approved (October 2003) phosphate ester prodrug of amprenavir.

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**Figure. SOLO Study: Patients Achieving Viral RNA \(<400\) copies/mL at 48 Weeks**

The SOLO Study compared fosamprenavir (“908”; 1400 mg) plus ritonavir (200 mg) once daily versus nelfinavir (1250 mg) twice daily in ART-naive patients who also received background therapy with abacavir/lamivudine. The proportion of patients achieving viral loads \(<400\) copies/mL was similar in both groups, with a trend toward greater efficacy in the 908 group in patients with baseline viral loads \(>500,000\) copies/mL (A). In patients with very low \(<50\) cells/mm\(^3\) CD4 counts, 908 plus ritonavir once daily achieved the primary endpoint \(<400\) copies/mL HIV-1 RNA) in a greater proportion of patients compared with ritonavir (B).

Intention to treat; RD = F.

* Post hoc exploratory analysis.

Adapted from Schurmann et al.12

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Long-term potency must include a consideration of side effects, which can create a barrier to realizing the potential of an agent.
The agent is formulated as a 700-mg tablet that may be dosed either once or twice daily and may be administered in boosted or unboosted fashion.

Three pivotal clinical trials of 908 have been conducted in ART-naive and ART-experienced patients (Table). Final 48-week results of NEAT found that unboosted 908 (1400 mg) given twice daily compared with nelfinavir (1250 mg) twice daily in an ART-naive patient population (nearly 50% had baseline viral loads >100 000 copies/mL) resulted in a greater proportion of subjects achieving an undetectable viral load with 908. SOLO was a study of once-daily 908 (1400 mg) plus ritonavir (200 mg) in ART-naive patients (nearly one fifth had baseline CD4 counts <50 cells/mm3). Similar efficacy of the boosted 908 regimen compared with a regimen containing standard-dose nelfinavir was shown in final 48-week results. In SOLO, stratification by baseline viral load showed the comparable efficacy of both arms, with a trend toward greater efficacy with boosted 908 treatment in patients with very high baseline viral loads of greater than 500 000 copies/mL (Figure, A). Similarly, once-daily 908 in combination with ritonavir performed slightly better overall compared with nelfinavir but, in those with baseline CD4 cell counts of less than 50 cells/mm3, was shown to achieve the primary endpoint in 73% of patients compared with 51% of patients in the nelfinavir twice-daily arm (Figure, B).

A third study, CONTEXT, evaluated 2 different dosing strategies of ritonavir-boosted 908—1400 mg with 200 mg ritonavir once daily or 700 mg with 100 mg ritonavir twice daily—versus standard-dosed lopinavir/ritonavir in ART/PI-experienced patients. At 24 weeks, both 908 plus ritonavir arms and the lopinavir/ritonavir arm demonstrated comparable, potent efficacy: for example, a slightly greater proportion of patients taking lopinavir/ritonavir twice daily (64%) achieved vRNA of less than 50 copies/mL compared with 59% for those taking twice-daily 908 plus ritonavir. Forty-eight-week results from the CONTEXT study are expected soon. Clinically significant implications of these phase 3 studies are that 908 may offer potent and flexible dosing options for ART-naive patients—either unboosted (NEAT) or boosted (SOLO), depending on the patient’s needs. In experienced patients (CONTEXT), while further analyses of final results are necessary, the trend toward better virologic outcome with a twice-daily boosted 908 regimen (compared with once-daily boosted 908) suggests this new PI may offer a good alternative option for anti-HIV therapy in this patient population (see article by Dr Mallal, in this issue).

**Tipranavir**

First in a new PI-subclass, the nonpeptidic PIs (NPPIs), tipranavir began phase 3 trials in 2003. The agent has shown activity against many viral strains that are resistant to the existing PIs. Tipranavir is being evaluated only in boosted form for pharmacokinetic reasons (poor bioavailability). Boosting may allow tipranavir to be dosed twice daily with a reduced pill burden.

Dose-ranging trials have shown that doses of tipranavir/ritonavir that are 500 mg/100 mg twice daily or greater are associated with a 1.3- to 1.4-log reduction in viral load in single-PI–experienced patients and a 1.7- to 2.3-log decrease in multiple-PI–experienced patients (Table). A study in PI-experienced patients evaluating 3 different doses of tipranavir/ritonavir revealed a median change in viral load ranging from –1.10 log to –0.32 log for tipranavir concentrations of less than 20 µM to 2 µM or less. Based on the combined results of these studies, tipranavir/ritonavir 500 mg/200 mg twice daily was selected for evaluation in phase 3 trials (RESIST 1 and RESIST 2).

**TMC-114**

TMC-114 is also an NPPI. It has demonstrated activity against HIV-1 strains resistant to existing PIs, including multidrug-resistant strains. Similar to tipranavir, this agent is also being studied in boosted form only, although no final dosing formulation has yet been defined.

A phase 2 dose-ranging study of TMC-114 in combination with ritonavir examined 3 different doses of the drug in PI-experienced patients (300 mg TMC-114 plus 100 mg ritonavir twice daily, 600 mg plus 100 mg twice daily, 900 mg plus 100 mg once daily; Table). Greater than 1-log viral load reductions were seen at all 3 doses, although the greatest vRNA reduction was for those taking the 600 mg TMC-114 plus 100 mg ritonavir twice daily (–1.5 log).
Conclusion

The specific roles for each of the new PIs—atazanavir, 908, tipranavir, and TM C-114—is yet to be determined. Both atazanavir and 908 have shown efficacy in ART-experienced and ART-naive patients. Tipranavir and TM C-114, each in combination with ritonavir, may be more appropriate in the salvage setting; no data in ART-naive patients exist yet for these 2 agents. The improvements in effective potency with the new PIs that permit less frequent dosing, reduced pill burdens, along with at least equivalent or even greater efficacy compared with older PIs should offer patients better options for achieving treatment success and improved quality of life.

REFERENCES


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