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Amprenavir

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Contents

Summary

▲ Amprenavir is a viral protease inhibitor with specificity for the HIV protease enzyme. The resistance profile of amprenavir appears to differ from that of other protease inhibitors such as saquinavir and indinavir.

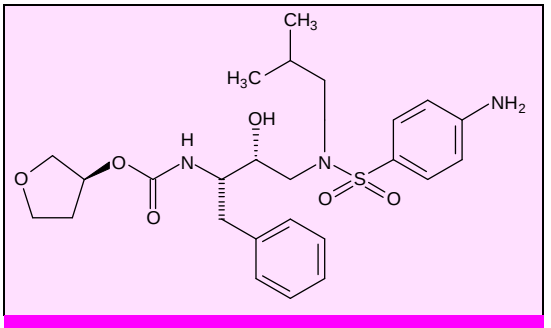
▲ Twelve hours after single-dose administration of amprenavir 1200mg to HIV-infected individuals, the mean plasma concentration of the drug was more than 10-fold greater than the 50% inhibitory concentration for HIV-1_{IIIB} in peripheral blood lymphocytes.

▲ In a small nonblind study, amprenavir monotherapy increased CD4+ cell count and decreased viral load in 37 patients with HIV infection and no previous exposure to protease inhibitor therapy.

▲ Combination therapy comprising amprenavir and other antiretroviral agents (abacavir, zidovudine, lamivudine, indinavir, saquinavir or nelfinavir) decreased viral load and increased CD4+ cell counts in patients with HIV infection. Antiviral efficacy was maintained during up to 24 weeks' follow-up.

▲ Available data suggest that rash, headache and diarrhoea or loose stools are the most frequent adverse events associated with amprenavir therapy.

Features and properties of amprenavir (141W94, VX-478)	
Indications	
HIV infection	
Mechanism of action	
Antiviral	HIV protease inhibitor
Anti-HIV activity	
Concentration inhibiting 50% of clinical isolates	0.012 μmol/L (zidovudine-sensitive), 0.019 μmol/L (zidovudine-resistant)
Dosage and administration	
Usual dosage used in clinical trials	1200mg twice daily
Route of administration	Oral
Pharmacokinetic profile	
Mean plasma concentration 12h after single-dose administration of 1200mg	0.64 mg/L
Time to peak plasma concentration	1.1-2.1h
Elimination half-life	9h
Adverse events	
Most frequent	Rash, diarrhoea or loose stools, headache



Amprenavir (141W94, VX-478)

Amprenavir is an orally active nonpeptide inhibitor of the HIV aspartic protease enzyme. This enzyme plays an essential role in the post-translational processing of the *gag* and *gag-pol* gene products into key structural proteins and replication enzymes of HIV. Inhibition of HIV protease, therefore, results in the inhibition of processes necessary for viral maturation and proliferation.[1]

1. Pharmacodynamic Profile

In Vitro Anti-HIV Activity

- Amprenavir was >5000-fold more selective for viral than for human aspartic protease.[2] It demonstrated minimal cytotoxicity against a wide range of human cell lines (50% toxic concentration >50 μmol/L),[2,3] and assessment of genetic toxicity using the Ames salmonella/mammalian microsome mutagenicity assay showed no drug-related changes at amprenavir concentrations ≤5000 μg/plate.[2]

- The antiviral activity of amprenavir is specific for HIV. At concentrations ≤100 μmol/L, amprenavir showed no inhibitory activity against several other viruses including herpes simplex virus types 1 and 2 and varicella zoster virus.[3]

- The concentrations of amprenavir producing 50% inhibition (IC_{50}) of HIV-1_{IIIB} in MT4 cells (T cell line) and peripheral blood lymphocytes were 0.084 and 0.08 μmol/L, respectively.[4,5]

- In MT4 cells acutely infected with HIV-1_{IIIB}, amprenavir produced synergistic inhibition (measured as the fractional inhibitory concentration against HIV-1_{IIIB}) in combination with the reverse transcriptase inhibitors zidovudine, didanosine, raluridine, abacavir or 524W91, or the protease inhibitor saquinavir. Amprenavir had an additive inhibitory effect with the protease inhibitors indinavir or ritonavir.[6]

- In the presence of 45% human plasma or serum, the antiviral activity of amprenavir [expressed as IC_{50} and 90% inhibitory concentration (IC_{90})] against HIV_{IIIB} infection in the CEM T cell line was reduced by 1.4- to 2-fold compared with control experiments in the presence of 15% foetal bovine serum.[7] At α_1-acid glycoprotein levels approximating those in normal human plasma (18 μmol/L) or plasma from patients with HIV infection (27 μmol/L), the IC_{50} of amprenavir was increased by 3- to 5-fold and the IC_{90} of the drug was increased by 1.5- to 1.8-fold in this cell line (*vs* the same control).[7] However, despite significant plasma protein binding, the free amprenavir concentration (0.2 μmol/L) exceeded the IC_{90} value (total drug concentration 2.0 μmol/L).[7]

- Incubation of amprenavir with α_1-acid glycoprotein 2 g/L in MT2 cells (T cell line) and lymphocytes increased the IC_{50} of amprenavir by 18- and 49-fold, respectively, and the IC_{90} of the drug by 16- and 37-fold, respectively, compared with incubation without α_1-acid glycoprotein.[8]

Viral Resistance

- *In vitro* serial passage studies suggest that a mutation at codon 50 of the HIV-1 protease substrate binding site is central to the development of resistance to amprenavir. This mutation confers an approximately 2-fold reduction in susceptibility to the drug. A double mutation at codons 46 and 50 was associated with a 3- to 7-fold reduction and a triple mutation at codons 46, 47 and 50 was associated with an approximately 14-fold reduction in sensitivity to amprenavir.[9,10]

- HIV-1 isolates resistant to amprenavir showed limited cross-resistance to saquinavir or indinavir

in vitro.[9,10] The IC_{50} values of amprenavir against 6 zidovudine-sensitive and 3 zidovudine-resistant isolates *in vitro* were 0.012 and 0.019 μmol/L, respectively.[6] In comparison, the respective mean IC_{50} values for zidovudine against zidovudine-sensitive and zidovudine-resistant isolates were 0.19 and >10 μmol/L.[3]

- There was no evidence of resistance in clinical isolates from 42 patients treated with amprenavir (≤2400 mg/day) for 4 weeks.[11]

2. Pharmacokinetic Profile

- In a Japanese single-dose pharmacokinetic study in healthy fasting volunteers, the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) were directly proportional to the dose of amprenavir (150 to 1200mg). C_{max} values of 1.7 and 6.3 mg/L were achieved after single-dose administration of amprenavir 300 and 900mg, respectively.[12] Time to C_{max} (t_{max}) varied from 1.1 to 2.1 hours.[6]

- Twelve hours after single-dose administration of amprenavir 1200mg to HIV-infected volunteers, the mean plasma concentration of the drug (0.64 mg/L) was more than 10 times greater than the *in vitro* IC_{50} for HIV-1_{IIIB} in peripheral blood lymphocytes.[4]

- Compared with fasting healthy volunteers, nonfasting individuals receiving a single dose of amprenavir 600mg experienced a 2.5-fold increase in t_{max} and a decrease of 46 and 23%, respectively, in C_{max} and AUC.[12] Plasma concentrations of amprenavir 600mg were maintained above the IC_{90} for approximately 18 hours under nonfasting conditions.

- In patients who received amprenavir 300mg twice daily for 28 days, the average steady-state plasma trough concentration (just before the next dose) exceeded the IC_{90} (value not provided), and mean steady-state C_{max} was 30-fold greater than the IC_{90}.[5,13] The mean plasma elimination half-life of amprenavir was approximately 9 hours.

- When administered orally to rats, amprenavir penetrated a wide range of tissues.[3]

- Amprenavir is approximately 90% bound to human plasma proteins, predominantly to α_1-acid glycoprotein.[7] Binding of amprenavir to α_1-acid glycoprotein is relatively weak (dissociation constant 4 μmol/L; dissociation rate 100 sec^{-1}).[7]

- Available data from *in vitro* and *in vivo* studies in animals suggest that amprenavir undergoes limited hepatic metabolism and is excreted predominantly via the biliary route.[2,14] In human liver microsomes, amprenavir inhibited cytochrome P450 (CYP) 3A4 and CYP2C19 isoenzyme activity but had a minimal inhibitory effect on the isoenzymes CYP1A2, 2C9, 2D6 or 2E1.[15] The magnitude of the inhibitory effect of amprenavir for CYP3A4 was less than that of ritonavir, similar to that of indinavir and nelfinavir and greater than that of saquinavir.

Drug Interactions

- Ritonavir inhibited the cytochrome P450-mediated metabolism of amprenavir in rat and human liver microsomes *in vitro*.[16] Oral coadministration of ritonavir 10 mg/kg and amprenavir 10 mg/kg to rats increased the AUC and C_{max} of amprenavir by 8- and 1.8-fold, respectively, versus monotherapy values.[16]

- After single-dose coadministration of amprenavir 1200mg and the CYP3A4 inhibitor ketoconazole 400mg to healthy volunteers, the $AUC_{0-\infty}$ values of each agent were increased by 32 and 44%, respectively, compared with values obtained after monotherapy.[17] This effect was probably attributable to competition for the CYP3A4 isoenzyme.

- Clinically significant pharmacokinetic drug interactions do not appear to occur during coadministration of amprenavir and abacavir.[18,19]

3. Therapeutic Trials

- In a nonblind phase I/II study, 37 HIV-infected patients (CD4+ cell count 150 to 400 cells/μl) with no previous exposure to protease inhibitor therapy were treated with amprenavir monotherapy 300 (n = 9), 900 (n = 9) or 1200mg twice daily (n = 7)

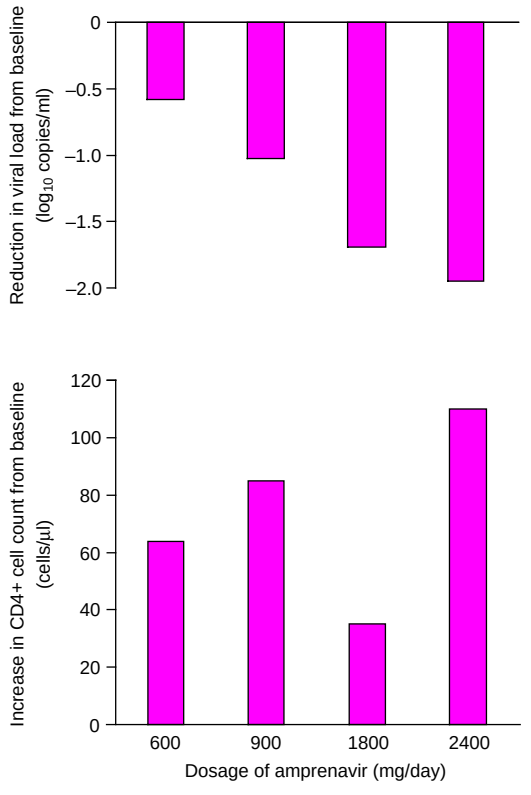


Fig. 1. Clinical efficacy of amprenavir. Median maximum reduction in viral load (log_{10} copies/ml) and increase in CD4+ cell count (cells/μl) in 37 patients with HIV infection (CD4+ cell count 150 to 400 cells/μl) treated with amprenavir 600 (n = 9), 900 (n = 12), 1800 (n = 9) or 2400 mg/day (n = 7) for 4 weeks in a nonblind study.[20]

or 300mg 3 times daily (n = 12) for 4 weeks.[20] Median CD4+ cell count increased by 35 to 110 cells/μl and median viral load decreased by 0.58 to 1.95 log_{10} copies/ml from baseline (fig. 1).

Combination Therapy

- In a nonblind observational study, HIV-1 RNA plasma levels showed a rapid (over 2 to 4 weeks) and marked decline from baseline and reached undetectable levels in 28 of 35 antiretroviral-naive patients treated with amprenavir 1200mg and abacavir 300mg, both administered twice daily.[21] When a more sensitive viral assay was used (limit of detection 5 copies/ml) for samples from 11 patients followed up for 24 weeks, 9 patients had viral levels <50 copies/ml and 6 patients had viral levels <5 copies/ml. By week 24, mean CD4+ cell counts had increased by 187 cells/μl, mean CD8+ cell counts had decreased by 388 cells/μl and the percentages of CD4+ and CD8+ cells in the lymph nodes were normalised.

- Amprenavir (900, 1050 or 1200mg twice daily) was used in combination with zidovudine and lamivudine in 80 patients in a phase II study.[22,23] Initial data from this trial showed that after 12 weeks, amprenavir 1200mg twice daily in combination with zidovudine and lamivudine (dosages not specified) produced a median reduction in viral load from baseline of 2.65 log_{10} copies/ml (>99.8%); this compared with a reduction of 1.33 log_{10} copies/ml with zidovudine plus lamivudine therapy. Approximately 70% of all patients treated with the triple combination experienced a reduction in HIV viral load to below the limit of detection (<400 copies/ml of blood).

- Combination therapy comprising unspecified dosages of amprenavir plus indinavir, saquinavir, nelfinavir or zidovudine and lamivudine was administered to patients with no previous exposure to protease inhibitor therapy and a CD4+ cell count >200 cells/μl.[24] Viral levels were reduced by a median of 1.84 to 3.75 log_{10} copies/ml from baseline after 16 weeks of treatment (fig. 2).

Using an ultrasensitive assay for HIV RNA, undetectable virus levels (<20 copies/ml) were reported at 16 weeks in 4 of 6 patients who received amprenavir plus indinavir, 2 of 5 who received amprenavir plus saquinavir, 3 of 6 who received amprenavir plus nelfinavir and 2 of 3 who received amprenavir, zidovudine and lamivudine.

- HIV RNA levels were reduced from baseline by a median of 2.42 log_{10} copies/ml in 13 patients treated with amprenavir 1200mg plus abacavir 300mg, both administered twice daily for 16 weeks; 11 of these patients (85%) had undetectable virus levels (<400 copies/ml) after this time.[25,26] Corresponding median reductions in viral load ranged from 1.63 to 2.49 log_{10} copies/ml among a further 44 patients treated with abacavir plus the

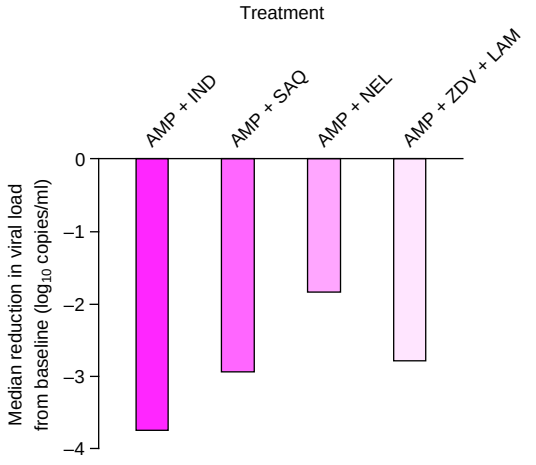


Fig. 2. Clinical efficacy of combination antiretroviral regimens containing amprenavir. Median reduction in viral load (log_{10} copies/ml) in patients treated with amprenavir (AMP) in combination with the protease inhibitors indinavir (IND), saquinavir (SAQ) or nelfinavir (NEL) or the reverse transcriptase inhibitors zidovudine (ZDV) and lamivudine (LAM) [dosages not specified] for 16 weeks.[24]

protease inhibitors indinavir (800mg 3 times daily), nelfinavir (750mg 3 times daily), saquinavir (1200mg 3 times daily) or ritonavir (600mg twice daily) and 54 to 78% of patients had undetectable viral loads. Patients recruited to this study were antiretroviral therapy naive and had a CD4+ cell count >100 cells/μl.

- Mean HIV RNA plasma levels were reduced by 2.26 log_{10} copies/ml from baseline after 8 weeks in 10 patients with chronic HIV infection treated with a 4-drug regimen comprising amprenavir (1200mg), abacavir (300mg), zidovudine (300mg) and lamivudine (150mg), all administered twice daily.[27] Mean CD4+ cell count increased by 126 cells/μl after week 12. In an additional 10 patients with acute HIV infection (<90 days) treated with this regimen, plasma viral load was reduced by 2.61 log_{10} copies/ml from baseline at week 8 and CD4+ cell count was increased by 172 cells/μl at week 12.[27] When patients with acute and chronic HIV infection were considered together, plasma HIV RNA levels were undetectable (<100 copies/ml) in 14 of 20 patients at week 8 and in 5 of 8 patients at week 20. All patients recruited to this study had no previous exposure to protease inhibitor therapy or lamivudine.

4. Tolerability

- Amprenavir monotherapy (≤2400 mg/day) was well tolerated in 37 patients treated for 4 weeks.[20] Adverse events developing in >10% of patients were generally mild and included rash, diarrhoea or loose stools and headache. Premature discontinuation of amprenavir was necessary in 3 patients, 2 because of rash and 1 because of worsening of chronic colitis.

- The most frequent adverse events reported in patients with HIV infection treated with combination antiretroviral regimens containing amprenavir were nausea, vomiting, diarrhoea, epigastric pain, perioral tingling/numbness, abdominal pain, flatulence, paraesthesia, headache, rash and fatigue.[21,22,24,25,27] However, it was not possible to determine whether these adverse events were attributable to amprenavir therapy or to the other agents included in the treatment regimens (abacavir, lamivudine, zidovudine, nelfinavir, indinavir and saquinavir).

- Adverse events associated with combination therapy comprising amprenavir (1200mg twice daily) plus abacavir (300mg twice daily) were generally mild and usually developed and sometimes worsened during the first 2 weeks of therapy.[21] An erythematous or maculopapular rash was the only serious adverse event reported among 35 patients treated with this regimen for up to 24 weeks. This adverse event developed in 5 patients, 6 to 9 days after the initiation of therapy, and necessitated treatment cessation in 2 patients.

5. Amprenavir: Current Status

Amprenavir is an HIV protease inhibitor in late phase clinical development. Amprenavir has shown promising clinical efficacy in initial studies in patients with HIV infection, and the results of ongoing clinical trials are awaited with interest.

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