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Abacavir

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Summary

▲ Abacavir is a nucleoside analogue reverse transcriptase inhibitor that inhibits clinical isolates of HIV *in vitro* with a potency similar to that of zidovudine.

▲ Resistance to abacavir develops relatively slowly. Cross-resistance between abacavir and didanosine, zalcitabine or lamivudine, but not zidovudine or stavudine, has been reported *in vitro*.

▲ Abacavir has good oral bioavailability, as demonstrated in animals, and penetrates the CNS.

▲ Treatment with abacavir, alone or in combination with other anti-HIV agents (zidovudine, lamivudine, nevirapine, amprenavir and/or other protease inhibitors), decreased viral load and increased CD4+ cell count in patients with HIV infection. Effectiveness was maintained for at least 48 weeks.

▲ In early phase I/II trials, headache, gastrointestinal disturbances, rash, malaise, fatigue and/or asthenia were the most common adverse events reported with abacavir alone or in combination with other anti-HIV agents. Hypersensitivity reactions lead to discontinuation of therapy in 2 to 3% of patients.

Features and properties of abacavir (1592U89)	
Indications	
HIV infection	Phase III
Mechanism of action	
Antiretroviral	Nucleoside analogue HIV reverse transcriptase inhibitor
Dosage and administration	
Usual dosage in clinical trials	600-1200 mg/day
Route of administration	Oral
Frequency of administration	2 *or* 3 times daily
Pharmacokinetic profile	
Peak plasma concentration	3.3 mg/L after 400mg 3 times daily
Time to peak plasma concentration	0.7-1.7h
Area under the plasma concentration-time curve	7.1 mg/L • h after 400mg 3 times daily
Bioavailability	76-100% in animals
Elimination half-life	0.8-1.5h
Adverse events	
Most frequent	Gastrointestinal disturbance, headache, rash, malaise, asthenia and/or fatigue

Abacavir (1592U89)

When starting treatment for HIV infection, the aim is to reduce plasma viral load to as low as possible (preferably to undetectable levels) for as long as possible.[1,2] Combination therapy is recommended to achieve this goal and minimise the development of drug resistance.

For initial treatment of HIV infection, triple-drug regimens comprising reverse transcriptase inhibitors plus protease inhibitors are currently preferred.[1,2] The efficacies of other regimens are less reliable or less well established.[1,2]

Abacavir was selected for further development after evaluation of a wide variety of carbocyclic nucleoside analogues with modifications designed to optimise *in vitro* anti-HIV potency, oral bioavailability and CNS penetration.

1. Pharmacodynamic Profile

In Vitro Anti-HIV Activity

- Abacavir is anabolised by a unique intracellular mechanism to form carbovir triphosphate (see section 2), which potently and selectively inhibits HIV reverse transcriptase; the mean K_i for inhibition of incorporation of dGTP into DNA by HIV-1 reverse transcriptase was 0.021 μmol/L.[3] The mean K_i values for inhibition of mammalian DNA polymerases α, β, γ and ε were 90 to 2900 times higher than those for HIV reverse transcriptase.

- Abacavir inhibited HIV-1 isolates from antiretroviral drug-naive patients [mean 50% inhibitory concentration (IC_{50}) 0.26 μmol/L] with similar potency to zidovudine (0.23 μmol/L) and greater potency than didanosine (0.49 μmol/L), but it was less potent than zalcitabine (0.03 μmol/L) in this assay.[3]

- In MT4 cells (T cell line), the *in vitro* anti–HIV-1_{IIIB} activity of abacavir (IC_{50} 4 μmol/L) was approximately 4-fold more potent than that of didanosine (17 μmol/L), approximately 2-fold less potent than zalcitabine (1.6 μmol/L) and lamivudine (2.1 μmol/L) and 100-fold less potent than zidovudine (0.04 μmol/L).[3]

- Abacavir showed strong synergistic *in vitro* activity against HIV-1_{IIIB} when combined with zidovudine, the non-nucleoside reverse transcriptase inhibitor nevirapine and the protease inhibitor amprenavir (141W94; VX-478) in MT4 cells.[3,4] Abacavir had additive and/or some synergistic effects with the nucleoside analogues didanosine, zalcitabine, stavudine and lamivudine.[3]

- The *in vitro* activity of abacavir against HIV-2 was similar to that against HIV-1_{IIIB}.[3] Abacavir (≤100 μmol/L) had some activity against hepatitis B virus, but not against herpes simplex virus type 1 or 2, varicella zoster virus or influenza A virus.

- Abacavir had relatively low cytotoxicity against human leukaemic cell lines, hepatitis B virus-producing liver tumour cell lines and bone marrow progenitor cells *in vitro* (IC_{50} generally >100 μmol/L).[3] The potential for haematopoietic toxicity was less than that of zidovudine. Mitochondrial DNA synthesis in Molt-4 cells was not inhibited by abacavir 100 μmol/L.

Viral Resistance

- Resistant virus is not rapidly selected for by abacavir *in vitro*.[5] A significant decrease in susceptibility to abacavir (i.e. 4- to 10-fold increase in IC_{50}) in wild-type or zidovudine-resistant HIV-1 strains was not observed until after 8 to 10 passages in MT-4 cells. Four mutations within the HIV-1 reverse transcriptase coding region were identified (65R, 74V, 184V and 115F). At least 2 or 3 concomitant mutations were necessary for significant resistance.

• Possible *in vitro* cross-resistance between abacavir and didanosine, zalcitabine or lamivudine was evident with some overlapping mutations in the above study. However, there was little cross-resistance between abacavir and stavudine or zidovudine, and abacavir selected for mutations that have previously been shown to suppress the zidovudine resistance phenotype.[5]

• Susceptibility to abacavir was maintained in >95% of HIV isolates that were resistant to zidovudine alone, lamivudine alone or 1 to 3 other nucleoside analogues (didanosine, stavudine or zalcitabine) in a study that screened 943 HIV samples from patients, most of whom had been previously treated with zidovudine and/or lamivudine.[6] Sensitivity to abacavir was reduced when the isolates demonstrated resistance to ≥2 nucleoside analogues, one of which was zidovudine or lamivudine. A more profound decrease in susceptibility to abacavir was evident in isolates with resistance to zidovudine, lamivudine and at least 1 other nucleoside analogue.

• HIV isolates that are highly resistant to multiple nucleoside analogues are also resistant to abacavir.[6,7]

Viral Spread in the CNS

• Abacavir reduced viral spread within brain tissue in a severe combined immunodeficient mouse model of HIV-1 encephalitis.[8] Mice received 2 doses of abacavir before intracerebral inoculation of HIV-1-infected monocytes and were killed 1, 7 or 14 days later. The number of HIV-1-infected monocytes was 50 to 80% less in abacavir-treated mice than in untreated mice.

2. Pharmacokinetic Profile

• The influx of abacavir into human erythrocytes and T-lymphoblastoid CD4+ CEM cells is rapid and occurs by nonfacilitated diffusion.[9]

• Intracellularly, abacavir is phosphorylated by adenosine phosphotransferase to abacavir monophosphate.[10] A cytosolic enzyme then converts abacavir monophosphate to carbovir monophosphate. This is further phosphorylated by cellular kinases to the active moiety carbovir triphosphate.

• Abacavir is very water soluble and lipophilic.[3] Consequently, it has good oral bioavailability (76 to ≈100% in various animal studies)[3,11] and CNS penetration.[3]

• In patients with HIV infection, area under the abacavir plasma concentration-time curve (AUC) and maximum abacavir plasma concentration (C_{max}) under fasting conditions were dose-dependent over the dose range evaluated.[12-14] With single doses of 100 to 1200mg, mean AUCs increased from 1.1 to 33.1 mg/L · h and C_{max} values from 0.6 to 9.6 mg/L.[12] After 4 weeks' treatment with 200 or 400mg 3 times daily, mean AUCs were, respectively, 4.2 mg/L · h and 7.1 mg/L · h and C_{max} values were 2.2 and 3.3 mg/L.[13] Apparent oral clearance (CL/F) of abacavir decreased from 1.8 L/h/kg with a single dose of 100mg to 0.55 L/h/kg with 1200mg.[12] Food reduced the AUC by 5% and the C_{max} by 35% in a single-dose study.[12]

• Following single or multiple doses in adults or children, maximum plasma concentrations of abacavir were attained after a mean of 0.7 to 1.7 hours, and the mean half-life was 0.8 to 1.5 hours.[12-14]

• The pharmacokinetics of abacavir in children appear to be similar to those in adults.[14] Mean CL/F tended to be slightly higher in children aged 2 to 5 years (1.8 L/h/kg after 4 mg/kg and 1.3 L/h/kg after 8 mg/kg) than in those aged 6 to 13 years (1.5 and 1.0 L/h/kg, respectively) and the half-life tended to be shorter (0.8 and 1.0 hours *vs* 1.2 and 1.3 hours).

• According to preclinical data, oral abacavir is primarily metabolised to 5′-glucuronide and 5′-carboxylate compounds, with only about 11 to 13% of the dose being recovered as unchanged drug.[11] The main route of excretion is renal.

CNS Penetration

• In rats, the brain penetration of abacavir was similar to that of zidovudine,[3] which is the only approved agent that has proven clinical benefit in the treatment of CNS manifestations of HIV infec-

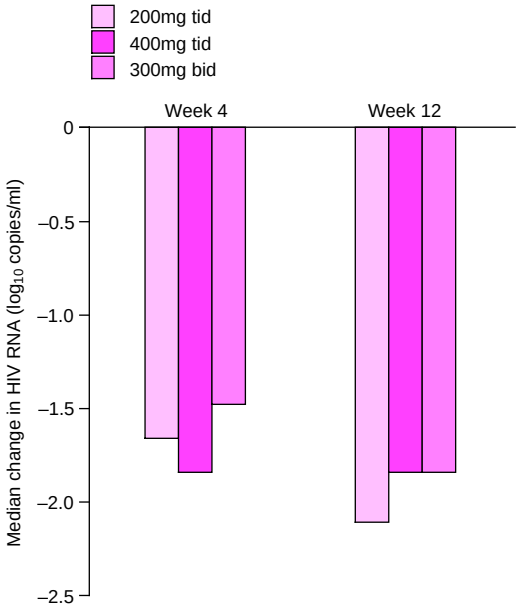

Fig. 1. Antiviral effect of abacavir in 47 patients with HIV infection.[19] Median change from baseline in HIV RNA (log_{10} copies/ml) after 4 and 12 weeks' treatment with oral abacavir 200 or 400mg tid or 300mg bid. From weeks 4 to 12, patients received zidovudine (dosage not stated) or placebo in addition to abacavir. Patients had baseline CD4+ cell counts of 200 to 500/μl and ≤12 weeks' previous treatment with zidovudine. *Abbreviations:* bid = twice daily; tid = 3 times daily.

tion. Detectable drug concentrations were maintained in rat brain for longer with abacavir than with zidovudine.[3] *In vitro* studies indicated that the brain penetration of abacavir is superior to that of most protease inhibitors.[15]

- The mean CSF to plasma abacavir concentration ratio was 18% 1.5 to 2 hours after administration of abacavir 200mg in HIV-infected patients who were receiving the drug 3 times daily.[15] The mean CSF abacavir concentration (0.5 μmol/L) in these patients was approximately twice that of the previously established IC_{50} for abacavir against clinical isolates of HIV-1 (0.26 μmol/L; see section 1).

Drug Interactions

- Preliminary data from studies in patients with HIV infection suggest that no clinically significant pharmacokinetic interactions occur between abacavir and amprenavir,[16,17] or zidovudine and/or lamivudine.[13,18]

- When a single dose of ethanol 0.7 mg/kg was coadministered with abacavir 600mg in patients with HIV infection the urinary recovery of the carboxylate metabolite of abacavir decreased by 62%, accompanied by a compensatory increase of 46% in the percentage of dose recovered as the glucuronide metabolite, compared with when abacavir was administered alone.[17]

- *In vitro* results suggest that abacavir does not significantly inhibit human liver microsomal cytochrome P450 (CYP) 3A4, CYP2C9 or CYP2D6 activity and is unlikely to interact with compounds that are metabolised by these enzymes.[17]

3. Therapeutic Trials

- HIV RNA decreased by a median of 1.48 to 1.84 log_{10} copies/ml (fig. 1) and CD4+ cell counts in-

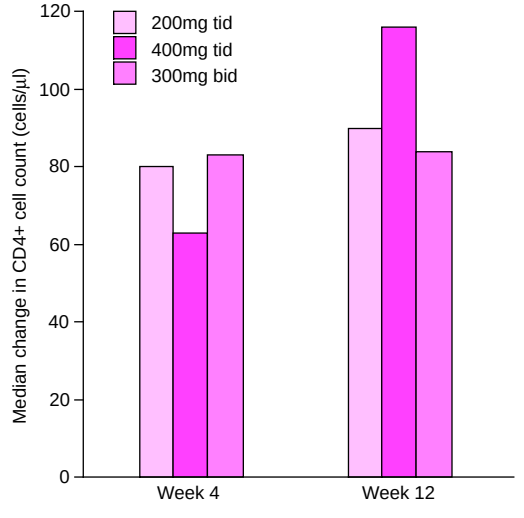

Fig. 2. Immunological response to abacavir in 54 patients with HIV infection.[19] Median change from baseline in CD4+ cell count after 4 and 12 weeks' treatment with oral abacavir 200 or 400mg tid or 300mg bid. From weeks 4 to 12, patients received zidovudine (dosage not stated) or placebo in addition to abacavir. Patients had baseline CD4+ cell counts of 200 to 500/μl and ≤12 weeks' previous treatment with zidovudine. *Abbreviations:* bid = twice daily; tid = 3 times daily.

creased by 63 to 83/μl (fig. 2) after 4 weeks' treatment with oral abacavir in patients with HIV infection.[19] Patients had baseline CD4+ cell counts of 200 to 500/μl, did not have AIDS and had limited (≤12 weeks) or no prior exposure to zidovudine. The decreased viral load and immunological response were maintained or enhanced during a further 8 weeks of treatment with abacavir plus either zidovudine (dosage not stated) or placebo.

- In the above study, mutations conferring resistance to abacavir developed in some patients who received monotherapy for the entire 12 weeks, but these mutations were not selected for in patients who received combination therapy with zidovudine from weeks 4 to 12.[20]

- HIV load was reduced to below the level of detection (<500 copies/ml) in all 19 patients who received abacavir 300mg twice daily plus the protease inhibitor amprenavir 1200mg twice daily for 8 weeks.[21] A more sensitive test in the 11 patients with data for 24 weeks' treatment revealed that viral levels were <50 copies/ml in 9 patients. Mean CD4+ cell counts increased by 187/μl and CD8+ cell counts decreased by 388/μl by week 24. Percentages of CD4+ and CD8+ cells in the lymph nodes normalised.

- Mean plasma HIV RNA levels were reduced by 2.26 $\log_{10}$ copies/ml after 8 weeks in 10 patients with chronic HIV infection who were treated with a 4-drug combination of abacavir 300mg, amprenavir 1200mg, zidovudine 300mg and lamivudine 150mg, all administered twice daily.[22] The mean increase in CD4+ cell count was 126 cells/μl after 12 weeks. Patients had baseline plasma HIV RNA levels of >5000 copies/ml and had not previously been treated with a protease inhibitor or lamivudine.

- The above study also involved 10 patients with acute HIV infection (<90 days).[22] In these patients, the mean reduction in viral load at week 8 was 2.61 $\log_{10}$ copies/ml and the mean increase in CD4+ cell count at week 12 was 172 cells/μl. When patients with acute and chronic infection were considered together, virus levels became undetectable (<100 copies/ml) in 14 of 20 patients by week 8 and in 5 of 8 patients treated for 20 weeks.

- Rapid declines in viral load were observed in 10 HIV-infected patients who received abacavir 600 mg/day, zidovudine 600 mg/day, lamivudine 300 mg/day, indinavir 3000 mg/day and nevirapine 400 mg/day.[23] From a median serum HIV-1 RNA level of 4.93 $\log_{10}$ copies/ml at baseline, levels declined to <400 copies/ml within 7 days of treatment. CD4+ cell counts increased from a mean of 320/μl at baseline to 434/μl after a mean of 4 months' follow-up.

- A combination regimen of abacavir 300mg twice daily plus 1 of 5 protease inhibitors (amprenavir 1200mg twice daily, indinavir 800mg 3 times daily, nelfinavir 750mg 3 times daily, saquinavir 1200mg 3 times daily or ritonavir 600mg twice daily) was administered to antiretroviral treatment-naive patients.[24,25] HIV RNA levels were reduced by a median of 1.63 to 2.49 $\log_{10}$ copies/ml (fig. 3). After 16 weeks' treatment, virus levels

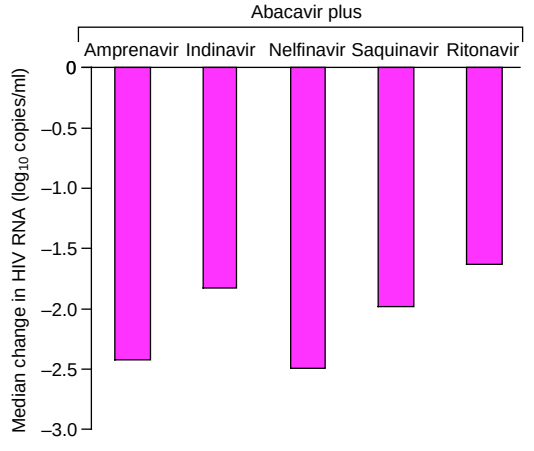

Fig. 3. Antiviral effect of abacavir plus a protease inhibitor.[24,25] Median change in HIV RNA levels ($\log_{10}$ copies/ml) from baseline in 57 HIV-infected patients treated for 16 weeks with abacavir 300mg twice daily plus one of the following protease inhibitors: amprenavir 1200mg twice daily, indinavir 800mg 3 times daily, nelfinavir 750mg 3 times daily, saquinavir 1200mg 3 times daily or ritonavir 600mg twice daily. Patients were antiretroviral treatment-naive and had baseline CD4+ cell counts >100/μl and HIV loads >5000 copies/ml.

were undetectable in 11 of 13 patients who received abacavir plus amprenavir, 7 of 10 who received abacavir plus indinavir, 7 of 9 who received abacavir plus nelfinavir, 7 of 13 who received abacavir plus saquinavir and 9 of 12 who received abacavir plus ritonavir. Patients had baseline CD4+ cell counts >100/μl and HIV loads >5000 copies/ml. The level of detection for HIV was not stated.

- Immunological data for week 16 of the above study showed that treatment with abacavir plus a protease inhibitor increased total CD4+ cell count by ≈170/μl.[26] Naive CD4+ and CD4+/28+ cell counts and circulating B lymphocyte levels also increased. Expression of CD38 and HLA DR were reduced towards normal.

- Abacavir reduced HIV load in patients who had been previously treated with zidovudine, stavudine, lamivudine and/or didanosine.[27] Nine of 15 patients had reductions in viral load of >1 $\log_{10}$ copies/ml 24 weeks after the addition of abacavir to their current nucleoside analogue therapy. A viral load response was observed in patients with isolates that had the 184V mutation and/or resistance to lamivudine. The response to abacavir was reduced or eliminated in patients with isolates with resistance to multiple nucleoside analogues.

- The development of resistance may have limited the response to abacavir in a study in which 47 heavily pretreated children received abacavir alone.[28,29] In this study, which was primarily designed to evaluate the pharmacokinetics of abacavir, children aged 3 months to 13 years discontinued their previous antiretroviral therapy and received only abacavir (4 mg/kg twice daily for 6 weeks and then 8 mg/kg twice daily for a further 6 weeks). Five of the 16 viral isolates tested developed new mutations during this monotherapy, but the drug will not be administered alone in clinical practice.

- The antiviral effect of abacavir is maintained for at least 48 weeks.[30,31] In one study, previously treatment-naive patients received abacavir with or without zidovudine for 12 weeks, followed by an abacavir-free period of up to 88 weeks before receiving extended treatment with abacavir in combination with other agents.[31] HIV levels were undetectable (<400 copies/ml) after 48 weeks of extended treatment in 8 of 15 patients who received abacavir plus nucleoside analogues and 9 of 10 who received abacavir plus protease inhibitors. In another study, virus levels were reduced below 400 copies/ml in 65% of the 46 evaluable patients after 48 weeks of abacavir treatment (4 to 24 weeks of abacavir alone then abacavir plus other antiretroviral therapy, most frequently zidovudine plus lamivudine).[30]

- In the above studies, CD4+ cell counts continued to increase during extended treatment with abacavir.[30,31]

- HIV RNA levels in the CSF were reduced by 1.22 $\log_{10}$ copies/ml after 3 to 8 weeks' treatment with abacavir 300mg, amprenavir 1200mg, zidovudine 300mg and lamivudine 150mg, all twice daily, in 5 patients.[22]

4. Tolerability

- The most commonly reported adverse events in clinical trials of abacavir in HIV-infected patients included nausea/vomiting, diarrhoea, headache, rash, malaise, asthenia and/or fatigue.[18-22,24,30,32] However, it is not clear whether these adverse events were solely attributable to abacavir or were partially or wholly attributable to the other agents administered concomitantly (including zidovudine, lamivudine, amprenavir and other protease inhibitors).

- In studies in HIV-infected patients in which abacavir was administered alone as a single oral dose, mild rash developed in 2 of 12 children (aged 2 to 13 years) who received 4 or 8 mg/kg,[14] and gastrointestinal disturbance was the primary adverse event in adults who received 100 to 1200mg.[12]

- The tolerability profile of abacavir in children is similar to that in adults.[29,33]

- Abacavir can cause a hypersensitivity reaction in 2 to 3% of recipients.[24] This is characterised by fever combined with nausea/vomiting, malaise

and/or rash, which typically occurs within 4 weeks of initiating therapy. The reaction resolves within a few days of treatment discontinuation. However, patients who experience this reaction should not resume abacavir treatment, as extremely severe and even fatal reactions have been reported under these circumstances.

5. Abacavir: Current Status

Abacavir is a nucleoside analogue reverse transcriptase inhibitor that is in late clinical development. It has shown efficacy in decreasing the viral load and increasing the CD4+ cell count in patients with HIV infection. Abacavir has an acceptable tolerability profile, although hypersensitivity reactions may limit its use in a small number of patients.

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