

Bevirimat

Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Bevirimat, also known as PA-457, is a betulinic acid derivative and a first-in-its-class maturation inhibitor. It is in Phase II studies to determine its use as a treatment for HIV and has been assigned fast-track status by the FDA as of January 2005. [1] [2] [3]

HIV/AIDS-Related Uses

Bevirimat is being evaluated as once-daily monotherapy for activity against HIV-1 in patients who are resistant to available treatments. Bevirimat was assigned fast-track status by the FDA as of January 2005.[4]

Pharmacology

Bevirimat is a first-in-its-class maturation inhibitor with potent activity against wild-type HIV-1 as well as against strains resistant to antiretroviral therapy. Maturation is a late stage in viral reproduction, involving Gag protein processing necessary for further infection of human cells. Bevirimat targets this late step and blocks conversion of the HIV-1 capsid precursor p25 to the mature capsid protein p24 in the CA-SP1 cleavage region. This results in the release of noninfectious viral particles and the termination of viral replication.[5] [6] SP1 is a small spacer peptide separating the CA and NC domains in the Gag polyprotein precursor. Bevirimat is specifically active at the CA-SP1 cleavage site.[7]

Amino acid residues in CA-SP1 Gag domains are critical for drug activity; thus, determinants that confer resistance map to this Gag domain.[8] An adenine (A) to valine (V) change at the first or third residues at the N-terminus of SP1 (A1V or A3V) resulted in a resistant phenotype.[9] However, genetic analysis of available patients showed no development of resistance, and bevirimat retained potency in patients with existing extensive mutations.[10]

Oral bevirimat is rapidly absorbed in animal models and in humans and has a half-life of nearly three days (60.3 hrs).[11] [12] A 10-day,

multiple-dose trial in healthy males evaluated daily doses of 25, 50, and 100 mg bevirimat. Peak plasma concentrations (C_{max}) at Day 10 were 7.98, 15.58, and 31.58 mcg/ml, respectively. Drug plasma levels accumulated approximately three- to fivefold from baseline. Areas under the concentration-time curve (AUC) at Day 10 were 156.5, 303.1, and 599.5 hr(mcg)/ml, respectively. The target minimum therapeutic concentration (C_{min}) of bevirimat was determined to be 2.3 mcg/ml and was achieved with single daily doses of 25 mg; tenfold target C_{min} concentrations were safely achieved with single daily doses of 100 mg.[13] Bevirimat demonstrated dose-related antiviral activity in a single-dose pharmacokinetic and -dynamic model and in a multiple-dose evaluation.[14] [15]

Bevirimat was nonteratogenic when administered orally in rats and rabbits. No developmental toxicity was observed up to the highest tested dosages of 900 mg/kg/day in the rat and 300 mg/kg/day in the rabbit. These dosages are approximately 44 and 29 times greater, respectively, than the potential human dosage for bevirimat of 200 mg/day.[16] Bevirimat is not oxidatively metabolized by the cytochrome P 450 (CYP) liver enzyme system. Testing of CYP enzymes 1A2, 2C9, 2C19, 2D6, and 3A4 showed no inhibition in human livers by the drug. Bevirimat is glucuronidated primarily by uridine 5'-diphosphate (UDP)-glucuronosyltransferase (UGT) 1A3 and weakly inhibits glucuronidation by some UGT isoforms.[17] Bevirimat displayed linear clearance in a three-cohort study of single 75, 150, or 250 mg doses.[18]

When tested against a panel of resistant HIV strains, bevirimat retained wild-type activity, whereas approved antiretroviral medications exhibited decreases in activity that ranged from several-fold to more than 100-fold.[19] Viral resistance to bevirimat was also examined in vitro, and five amino acid changes were identified that independently confer resistance: H226Y, L231M, and L231F at the C-terminus of CA; and A1V and A3V at SP1. The A3V/G225S mutant was fully drug resistant. The clustering of bevirimat resistance mutations at the CA/SP1 junction

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Pharmacology (cont.)

confirms that this region is the major target of bevirimat activity. Drug dependence observed for A3V mutations suggests multiple mechanisms of resistance. Viral resistance was not detected in vivo during a 10-day, multi-dose study that used standard genotyping methods.[20] Further resistance studies conducted in vitro have confirmed that mutations that confer resistance to bevirimat are found only at or near the site of the drug's mechanism of action: the capsid-SP1 cleavage site in the HIV Gag protein. The six in vitro mutations that induce resistance are CA-H226Y, L231M, and L231F, and SP1-A1V, A3V, and A3T. Bevirimat resistance may develop in the presence of pre-existing protease inhibitor mutations; however, a recent study suggests that PI-resistant mutants may be less likely than wild-type isolates to develop PA-457 resistance.[21] [22]

Genetic polymorphism in the Gag region of HIV resulted in viral resistance to bevirimat in a Phase II study of 88 HIV-infected patients. The polymorphism occurs in approximately 40% of clade-B HIV; pretreatment screening for the polymorphism may be necessary to identify patients who will respond to treatment with bevirimat.[23]

In a Phase I dose-evaluation trial, twenty-four healthy men received a single oral dose of bevirimat 25, 50, 100, or 250 mg. In each group, six men received active drug, and two men received placebo. Doses of bevirimat 50 mg or greater exceeded target plasma concentrations for more than 24 hours, establishing the possibility of once-daily therapeutic dosing.[24]

A single-dose, double-blind, placebo-controlled trial in twenty-four HIV infected patients with CD4 counts of 200 cells/ml or greater and viral loads of 5,000 to 250,000 copies/ml compared 75, 150, and 250 mg doses of bevirimat to placebo. All groups showed sustained decreases in viral load after 10 days. Viral load decreases appeared dose-dependent: approximately 70% reduction was achieved with bevirimat 250 mg; nearly 60% reduction with bevirimat 150 mg; and nearly 50% reduction with bevirimat 75 mg.[25]

A Phase IIa, double-blind, placebo-controlled trial examined daily doses of bevirimat 25, 50, 100, or 200 mg in HIV infected patients who were treatment-naïve for at least 12 weeks prior to the trial. Six patients received active drug in each dose group, and eight patients received placebo; all groups were treated for 10 days. The primary endpoint of demonstrated antiviral activity was evaluated on Day 11. Steady-state plasma concentrations were reached after approximately seven days of therapy. Bevirimat displayed dose-proportional pharmacokinetics: the 200 mg dose achieved a minimum serum concentration double that of the 100 mg dose. After a mild initial increase, viral load decreased significantly in the 100 and 200 mg dose groups compared with placebo. Day 11 median reductions were nearly threefold and approximately tenfold, respectively. In patients whose baseline viral loads were less than 100,000 copies/ml, median reductions with 100 and 200 mg doses were approximately threefold and 33-fold, respectively. Twenty-one of thirty-three patients showed no resistance to bevirimat.[26] [27]

In a Phase II, dose-finding study of bevirimat in 88 HIV-infected patients, only some patients responded to monotherapy treatment. Patients with adequate trough concentrations experienced maximal viral load decrease of approximately 20-fold after 7 days.[28]

A Phase IIb study was initiated in 2006 to study bevirimat in HIV infected patients who were failing current antiretroviral therapy. The primary endpoints included reduction in viral load after 14 days and after 3 months. In the first cohort, patients were administered bevirimat or placebo once daily for 3 months in combination with background antiretroviral therapy. A second, dose-escalation, cohort planned to enroll 12 treatment patients plus four placebo patients in three bevirimat once-daily dosage groups: 400, 500, and 600 mg.[29] Results from the first cohort showed an antiviral effect of bevirimat after 14 days of 400 mg daily dosing. At Day 15, the mean viral load reduction was approximately 60% in patients treated with 400 mg bevirimat. Two of 12 patients with drug-resistant HIV and treated with bevirimat achieved undetectable virus levels (HIV viral load less than 400 copies/ml), and one additional patient achieved

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Pharmacology (cont.)

viral load reduction of more than 90%. The overall plasma concentrations, and thus antiviral response, in the first cohort of bevirimat 400 mg was lower than expected, based on earlier bioavailability studies predicting concentrations similar to those seen in the Phase IIa study that used bevirimat oral liquid formulation. Data suggest the lower plasma concentrations resulted from the tablet formulation properties.[30] In March 2007, the manufacturer received FDA approval to continue revised dose-escalation cohorts in this study with the oral liquid formulation of bevirimat. In the first cohort, patients are being administered 14 days of bevirimat 250 mg monotherapy (eight patients) or placebo (two patients) once daily in the first cohort; primary endpoints are safety and efficacy (i.e., viral load reduction) of bevirimat at Day 15. Dose escalations of 50 mg are ongoing after completion of the first cohort.[31] In the 250 mg cohort, addition of bevirimat to failing background regimens reduced viral load by mean 0.68log on Day 15 and by .5log or greater in 71% of patients. Efficacy as measured by viral load reduction was greater than with the 400 mg tablet cohort, which had a mean viral load reduction of .036log. Mean steady state plasma concentrations were greater than those seen in earlier studies with the liquid formulation and were approximately double those seen with the tablet formulation of bevirimat 400 mg.[32] A 300 mg cohort was initiated, and eight patients received bevirimat. Mean viral load reduction was greater than in the 250 mg cohort at 1.02log; 75% of patients had greater than 0.5log and 63% had greater than 1log reduction on Day 15.[33] A bevirimat 350 mg cohort was initiated, in which nine patients received bevirimat and two received placebo. On Day 15, mean viral load was reduced 0.62log; 33% had greater than .5log reduction and were all greater than 1log. The area under the concentration-time curve and the steady state mean trough levels were similar in the 300 mg and 350 mg cohorts. The manufacturer intends to continue this Phase IIb trial with a 400 mg cohort.[34]

Adverse Events/Toxicity

Bevirimat was safe and well tolerated in a 10-day, double-blind, placebo-controlled trial in HIV

infected patients. Six patients were assigned to each dose level (25, 50, 100, and 200 mg), and eight patients were assigned to the placebo group. Adverse effects were mild to moderate; diarrhea with altered bowel habits was reported by one to six patients in each dose group and in five of eight patients in the placebo group. Grade 2 increases in triglyceride levels occurred in one patient on Day 5 but returned to baseline. No treatment-emergent drug-related Grade 3 or 4 adverse effects were seen. One patient with a 5-year history of poorly controlled hypertension experienced a probable transient lacunar cerebrovascular accident (CVA); this serious adverse event may not have been related to bevirimat administration.[35] [36] Two patients experienced mild adverse effects in the 300 mg cohort of an ongoing Phase IIb trial; bevirimat oral liquid formulation was well tolerated in both the 300 mg and 350 mg cohorts.[37] [38]

Drug and Food Interactions

Bevirimat does not inhibit the CYP liver enzyme system or interact with human p-glycoprotein.[39]

When tested with representative reverse transcriptase, protease, and fusion inhibitors, bevirimat exhibited nearly additive to strongly synergistic activity with each at 90% inhibitory concentrations against a panel of resistant viral strains.[40]

Because both bevirimat and atazanavir interact with the liver's UGT enzymes---bevirimat as a UGT substrate and weak inhibitor and atazanavir as an inhibitor---the combination was studied to determine possible pharmacokinetic interactions. Bevirimat and atazanavir serum concentrations appeared unaffected by concomitant administration, and bevirimat did not increase the hyperbilirubinemia that occurs with atazanavir because of its effect on the UGT system.[41]

Clinical Trials

For information on clinical trials that involve Bevirimat, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Bevirimat AND HIV Infections.

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Dosing Information

Mode of Delivery: Oral.[42]

Dosage Form: Bevirimat has been studied at once-daily doses of 25, 50, 75, 100, 150, 200, 250, 400, 500, and 600 mg.[43] [44] [45]

Both bevirimat 100 and 200 mg oral solutions have been studied in a Phase IIa trial, and a bevirimat 50 mg tablet to be used for 400 mg daily dosing has been studied in a Phase IIb trial. Early clinical bioavailability studies indicated that the tablet had approximately 60% of the oral bioavailability of an oral solution formulation. Thus, plasma concentrations after administration of a single 400 mg dose of bevirimat were expected to be comparable to those after administration of the bevirimat 200 mg oral solution. However, plasma concentrations with bevirimat 400 mg tablet dosing were actually about half what was expected and were more similar to concentrations achieved with bevirimat 100 mg oral solution dosing. Data suggest that the lower plasma concentrations result from properties of the bevirimat 50 mg tablet used in the Phase IIb trial.[46] Phase IIb studies are continuing but are using bevirimat oral liquid formulation in increasing dose cohorts.[47] In addition, the manufacturer is considering a tablet formulation for use in a planned Phase III trial.[48]

Chemistry

CAS Name: 3-O-(3',3'-dimethylsuccinyl)betulinic acid[49]

Molecular formula: C₃₆H₅₃O₆[50]

C_{77.1%},H_{8.1%},O_{14.7%}[51]

Molecular weight: 653[52]

Other Names

PA 457[53]

PA457 cpd[54]

PA-457[55]

BVM[56]

Further Reading

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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