

PA- 457



Drug Class: Opportunistic Infection and Other Drugs

Drug Description

PA-457, a betulinic acid derivative, is 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

PA-457 is being evaluated as once-daily monotherapy for activity against HIV-1 in patients who are resistant to available treatments or in those who are infected with wild-type virus.[4] [5]

Pharmacology

PA-457 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. PA-457 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.[6] [7] SP1 is a small spacer peptide separating the CA and NC domains in the Gag polyprotein precursor. PA-457 is specifically active at the CA-SP1 cleavage site.[8]

Amino acid residues in CA-SP1 Gag domains are critical for drug activity; thus, determinants that confer resistance map to this Gag domain.[9] 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.[10] However, genetic analysis of available patients showed no development of resistance, and PA-457 retained potency in patients with existing extensive mutations.[11]

Oral PA-457 is rapidly absorbed in animal models and in humans and has a half-life of nearly three days (60.3 hrs).[12] [13] A ten-day, multiple-dose trial in healthy males evaluated daily doses of 25, 50, and 100 mg PA-457. 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 PA-457 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.[14] PA-457 demonstrated dose-related antiviral activity in a single-dose pharmacokinetic and -dynamic model and in a multiple-dose evaluation.[15] [16]

PA-457 is not oxidatively metabolized by the cytochrome P450 (CYP) liver enzyme system. Testing of CYP enzymes 1A2, 2C9, 2C19, 2D6, and 3A4 showed no inhibition in human livers by the drug. PA-457 is glucuronidated primarily by uridine 5'-diphosphate (UDP)-glucuronosyltransferase (UGT) 1A3 and weakly inhibits glucuronidation by some UGT isoforms.[17] PA-457 displayed linear clearance in a three-cohort study of single 75, 150, or 250 mg doses.[18]

In a Phase I dose-evaluation trial, twenty-four healthy men received a single oral dose of 25, 50, 100, or 250 mg PA-457. In each group, six men received active drug and two men received placebo. Doses of 50 mg or greater exceeded target plasma concentrations for more than 24 hours, establishing the possibility of once-daily therapeutic dosing.[19]

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 PA-457 to placebo. All groups showed sustained decreases in viral load after ten days. Viral load decreases appeared dose-dependent: approximately 70% reduction was achieved with 250 mg PA-457; nearly 60% reduction with 150 mg PA-457; and nearly 50% reduction with 75 mg PA-457.[20]

A Phase IIa, double-blind, placebo-controlled trial examined daily doses of 25, 50, 100, or 200 mg in

Pharmacology (cont.)

HIV infected patients who were treatment-naive 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. PA-457 displayed dose-proportional pharmacokinetics: the 200 mg dose achieved a C_{min} double that of the 100 mg dose. After a mild initial increase, viral load decreased significantly in the 200 and 100 mg dose groups compared to placebo. Day 11 median reductions were approximately tenfold and nearly threefold, respectively. In patients whose baseline viral loads were less than 100,000 copies/ml, median reductions with 200 and 100 mg doses were approximately 33-fold and threefold, respectively. Twenty-one of thirty-three patients showed no resistance to PA-457.[21] [22] [23]

Adverse Events/Toxicity

PA-457 was safe and well tolerated in a ten-day, double-blind, placebo-controlled trial in HIV infected patients. 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 five-year history of poorly controlled hypertension experienced a probable transient lacunar cerebrovascular accident (CVA); this serious adverse event may not have been related to PA-457 administration.[24] [25]

Drug and Food Interactions

PA-457 does not inhibit the CYP liver enzyme system or interact with human p-glycoprotein.[26]

Clinical Trials

For information on clinical trials that involve PA-457, visit the ClinicalTrials.gov web site at

<http://www.clinicaltrials.gov>. In the Search box, enter: PA-457 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[27]

Dosage Form: PA-457 has been studied at once-daily doses of 25, 50, 75, 100, 150, 200, and 250 mg.[28] [29]

Chemistry

CAS Name: 3-O-(3',3'-dimethylsuccinyl)betulinic acid[30]

Molecular formula: C₃₆H₅₃O₆[31]

C_{77.1%},H_{8.1%},O_{14.7%}[32]

Molecular weight: 653[33]

Other Names

PA 457[34]

PA457 cpd[35]

Further Reading

Molecule of the month. PA-457. Drug News Perspect. 2004 May;17(4):283. No abstract available. PMID: 15334176

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Manufacturer Information

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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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