Capravirine, a Nonnucleoside Reverse-Transcriptase Inhibitor in Patients Infected with HIV-1: A Phase 1 Study

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Capravirine is a nonnucleoside reverse-transcriptase inhibitor (NNRTI) with a unique resistance profile. Although single mutations allow resistance to established NNRTIs, human immunodeficiency virus (HIV)–1 must undergo multiple mutations to achieve resistance to capravirine. In the present phase 1 study, capravirine was administered orally for up to 28 days to 55 HIV-1–infected individuals with $CD4^+$ T lymphocyte counts of 50–500 cells/μL. The most frequent adverse events were diarrhea (5%) and nausea (4%), with no drug-related rashes observed. The day 15 median (mean) HIV-1 load decreased by 1.34 (1.45) $\log_{10}$ copies/mL in the patients receiving 25 mg/kg/day. Capravirine demonstrated potent antiviral activity, even in antiretroviral-experienced patients.

The emergence of drug-resistant HIV-1 variants has closely followed the usage of antiretroviral compounds [1]. Mutations introduced during viral replication allow the outgrowth of mutant strains with diminished drug susceptibility, and resistance to all classes of antiretroviral drugs has emerged. The established nonnucleoside reverse-transcriptase inhibitors (NNRTIs) are particularly vulnerable to the development of viral resistance. NNRTIs function by allosterically inhibiting HIV reverse-transcriptase active-site catalytic aspartate residues, and several single reverse-transcriptase amino acid substitutions at or near the drug-binding pocket promote high-level NNRTI resistance [2–5]. The acquisition of mutations that bestow cross-resistance to all approved NNRTIs threatens their clinical utility [5–7]. Novel NNRTIs are therefore desirable for the treatment of the growing number of patients infected with resistant variants.

Capravirine (formerly known as "S-1153" and "AG-1549") is an imidazole NNRTI and may be an attractive alternative to currently available NNRTIs, particularly for the rescue of NNRTI-failing regimens [8]. Although functionally related to other NNRTIs, capravirine is structurally distinct. Capravirine forms an extensive hydrogen-bond network with the reverse-transcriptase main chain, a network that is unlikely to be disrupted by simple side-chain mutations [9]. In preclinical studies, capravirine potently inhibited the reverse transcriptase of several clinical isolates and demonstrated a 10–100-fold greater potency than that of nevirapine and delavirdine [8]. Capravirine has a 50% effective concentration (EC_{50}) in the nanomolar or subnanomolar range and maintains activity toward HIV-1 strains harboring commonly encountered mutations, including L100I, Y181C, and V106A. Importantly, in laboratory studies, capravirine maintains potent activity toward strains with the K103N mutation, which confers high-level resistance to all approved NNRTIs. Capravirine likewise maintains potent activity toward some strains with double NNRTI-associated mutations, including V106A/Y181C [8]. Furthermore, reverse transcriptase must undergo double or triple mutations to acquire high-level capravirine resistance, which promises to delay the appearance of capravirine-resistant variants [8]. Indeed, in laboratory studies, resistance has occurred slowly and required mutations that were distinct from characterized NNRTI-resistance mutations. In a mouse/MT-4 replication model, capravirine synergy was observed with zidovudine and other antiretroviral drugs [8].

Preclinical studies have shown no significant capravirine toxicity in rodents or canines when the drug was administered at levels exceeding the highest ones used in the present trial. Capravirine is metabolized by the cytochrome P450 enzyme CYP3A4; P450 inhibitors, including indinavir, ritonavir, and ketoconazole, may increase capravirine plasma concentrations. The primary objective of the present open-label, noncomparative, dose-finding study was to determine (1) the pharmacokinetic (PK) and toxicity profiles of capravirine and (2) the maximum-tolerated dose. A secondary objective was to search for early evidence of antiviral activity in NNRTI-naive, HIV-1–infected patients after oral administration of capravirine.

Patients, materials, and methods. Fifty-five HIV-1–infected patients were studied at 2 sites (Beth Israel Deaconess

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Medical Center, Boston, MA, and St. Francis Memorial Hospital, San Francisco, CA). All patients were NNRTI naive. Patients were allowed to continue nucleoside reverse-transcriptase inhibitor (NRTI) therapy, provided they had been on a stable drug regimen for at least 4 weeks before study entry. Previous protease inhibitor (PI) therapy was allowed, although it must have been discontinued at least 30 days before study entry. Inclusion criteria included a $CD4^+$ T lymphocyte count of 50–500 cells/μL, a Karnofsky performance status >60%, a negative pregnancy test, an absolute neutrophil count >1000 cells/μL, a hemoglobin level >9.0 mg/dL, a platelet count >75,000 cells/μL, an alanine aminotransferase and aspartate aminotransferase level <3.0 times the upper limit of normal (ULN), a bilirubin level <2.0 mg/dL, and a creatinine level <1.5 times the ULN. There was no entry criterion for HIV-1 load. Prophylactic therapy for *Pneumocystis carinii* pneumonia was required for patients whose $CD4^+$ T lymphocyte counts were <200 cells/μL. Exclusion criteria included an active opportunistic infection, pregnancy or lactation, and concurrent use of cytotoxic agents, immune therapy, other investigational compounds, drugs extensively metabolized by P450 cytochromes, or highly plasma protein–bound drugs with narrow therapeutic indices, including warfarin and phenytoin.

The human-experimentation guidelines of the US Department of Health and Human Services and of the authors' institutions were followed in the conduct of clinical research. The study was approved by the local institutional review boards (IRBs). Informed consent was obtained from patients—all patients signed an IRB-approved consent form before any study procedures were initiated.

For the present open-label, noncomparative, dose-finding study, patients were sequentially enrolled into 3 treatment groups. In the regimen 1 arm, 2 groups of 8 patients each received a single oral dose of capravirine at either 5 mg/kg or 7 mg/kg, to evaluate PK data. In the regimen 2 arm, 4 groups of 3 patients each received capravirine at either 5, 10, 15, or 20 mg/kg/day as 3 divided doses (every 8 h) for 14 days. In the regimen 3 arm, 3 groups of 9 patients each received capravirine at either 20 or 25 mg/kg/day as 2 divided doses (every 12 h) or at 25 mg/kg/day as 3 divided doses (every 8 h) for 28 days. Capravirine was administered orally as 25-mg capsules to patients in the regimen 1 and regimen 2 arms and as 100-mg capsules to patients in the regimen 3 arm.

The toxicity grading system of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, was used to report adverse events. Patients were evaluated by clinical laboratory tests and physical examination (on days 1, 8, 15, and 22 for the regimen 1 arm; on days 1, 8, 15, 22, and 43 for the regimen 2 arm; and on days 1, 8, 15, 22, 29, and 50 for the regimen 3 arm). For the regimen 2 and regimen 3 arms, blood samples were obtained for PK analysis before dosing; 0.3, 1, 2, 3, 4, 6, and 8 h after the first dose was administered; and 0, 0.3, 1, 2, 3, 4, 6, 8, 12, and 24 h after the last dose was administered. Blood samples were also obtained immediately before and 2 h after the midpoint dose (on day 8 for the regimen 2 arm and on day 15 for the regimen 3 arm). Capravirine plasma concentrations were determined by liquid chromatography/mass spectrometry/mass spectrometry. HIV-1 RNA plasma levels (lower limit of detection, 400 copies/mL) were measured on days 1, 8, 15, and 43 in the regimen 2 arm and on days 1, 8, 15, 22, 29, and 50 in the regimen 3 arm. $CD4^+$ T lymphocyte counts were measured on days 1, 15, and 29 in the regimen 3 arm.

For statistical analysis, the maximum drug concentration (C_{max}) and the time to maximum (peak) drug concentration were calculated. The dosing interval area under the curve (AUC) was calculated by use of the trapezoidal method. PK parameters were calculated by use of a 2-compartment linear model. Relevant half-lives were determined by use of a weighted, nonlinear least-squares model. PK parameters were analyzed by use of WinNonlin (Scientific Consulting), a commercially available modeling program. A significant change from baseline in HIV-1 load that represented a treatment effect was defined as >0.41 $\log_{10}$ copies/mL, on the basis of a previously reported AIDS Clinical Trial Group study [10].

Results. The present study was conducted during 1997–1998. Overall, 91% of the 55 patients were men, and 73% were white, 20% were African American, 5% were Hispanic, and 2% were of other ethnic origin. Eighty-nine percent had previously received antiretroviral therapy (ART), and 11% were ART naive; 49% were receiving concurrent ART at study entry. The baseline characteristics of patients were similar among the 3 arms. For brevity, only the characteristics of the patients in the regimen 3 arm (28-day trial) are presented in detail here. The mean age was 40 years (range, 28–61 years), 92% had received previous NRTI therapy (40% of whom were taking NRTIs at study entry), and 22% had received previous PI therapy. Per the protocol, no patient was taking a PI or NNRTI at study entry. The mean $CD4^+$ T lymphocyte count was 351 cells/μL (range, 47–550 cells/μL).

No dose-limiting toxicities were observed. The majority of reported adverse events were mild to moderate in severity and were deemed to be unrelated to the administration of capravirine. Only 1 grade 3 adverse event was judged to be possibly associated with capravirine—an elevated creatine kinase (CK) level on day 8, which returned to normal on day 15. The following 7 other reported grade 3 or 4 adverse events were deemed to be unrelated to the administration of capravirine by the study investigators: neutropenia (2 patients), increased CK level (1 patient), fever (2 patients), hypertriglyceridemia (1 patient), and arthralgia (1 patient). Six of these 7 events resolved without further treatment. The most common drug-related ad-

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Table 1. Summary of pharmacokinetic parameters for capravirine, by dose level for a 28-day course (the regimen 3 arm).

Daily dose, time	C_{max}, μg/L	T_{max}, h	$T_{1/2}\alpha$, h	$T_{1/2}\beta$, h	AUC, ng × h/mL
25 (8.3 TID) mg/kg					
Day 1	808 (547)	1.58 (0.93)	0.54 (0.30)	2.31 (1.23)	1832 (1422)
Day 29	1119 (897)	1.79 (1.03)	0.70 (0.52)	3.19 (1.65)	3063 (2493)
20 (10.0 BID) mg/kg					
Day 1	778 (589)	2.39 (1.24)	0.45 (0.27)	2.72 (1.53)	2085 (1713)
Day 29	1440 (67)	2.13 (1.17)	0.81 (0.35)	4.71 (2.20)	3990 (1895)
25 (12.5 BID) mg/kg					
Day 1	1893 (1252)	2.23 (1.29)	0.81 (0.36)	3.10 (0.98)	6289 (5156)
Day 29	2305 (1881)	2.47 (0.94)	0.69 (0.25)	5.74 (2.22)	8884 (7533)

NOTE. Data are median (SD) of values, unless otherwise noted. Nine patients received each daily dose. AUC, area under the curve; BID, twice daily; C_{max}, maximum drug concentration; $T_{1/2}\alpha$, terminal elimination half-life distribution phase; $T_{1/2}\beta$, terminal elimination half-life elimination phase; TID, 3 times a day; T_{max}, time to maximum drug concentration.

verse events of grade 2 severity or higher were mild, transient effects, including diarrhea (5%), nausea (4%), a metallic taste disturbance that was noted more frequently at higher dose levels, and sleep disturbance. No drug-related rashes were observed. The patterns of adverse events were similar at doses of 8.3 mg/kg every 8 h, 10 mg/kg every 12 h, and 12.5 mg/kg every 12 h.

Capravirine displayed dose-proportional PK over the ranges tested in the present study, although with some intra- and interpatient variability. C_{max} was achieved between 1 and 3 h after ingestion (data not shown). Multiple-dose PK findings were evaluated over 14- and 28-day courses in the regimen 2 and regimen 3 arms, respectively. In these 2 arms, there were no significant differences in PK values between the first and last days (data for the regimen 3 arm are presented in table 1). Capravirine terminal elimination half-life did not change significantly between the first and last doses. Repeat dosing did not suggest accumulation in plasma concentration or substantial changes in absorption.

Though limited by sample size, statistically significant anti-

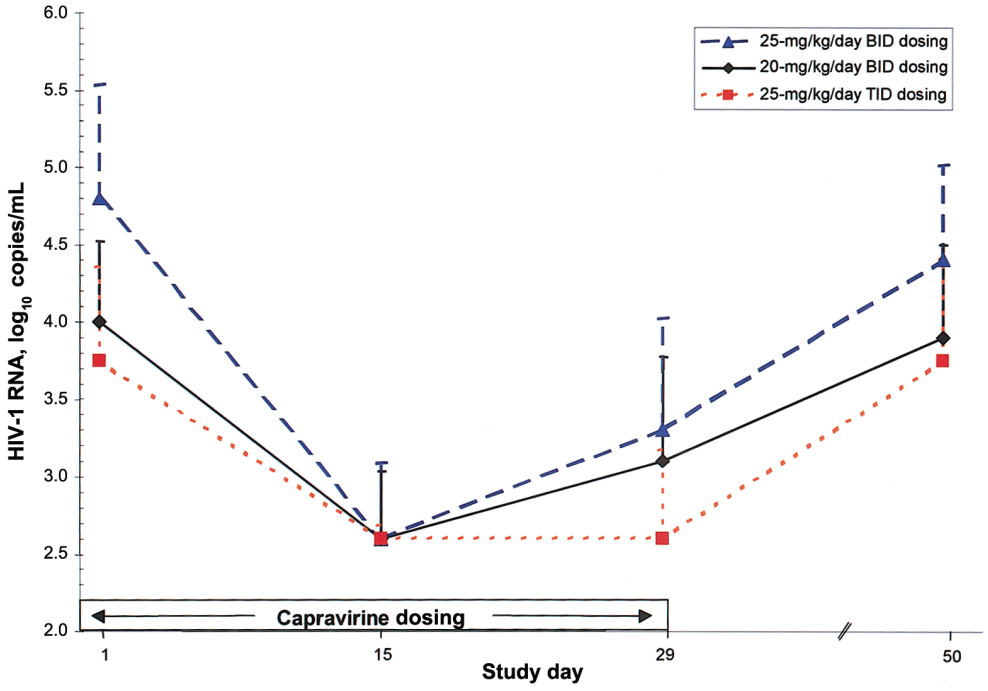

Figure 1. Median HIV-1 loads in the patients in the regimen 3 arm. Error bars represent 95% confidence intervals (only top halves are shown). The $\log_{10}$ HIV-1 RNA load of 2.60 represents the lower limit of detection (400 copies/mL). Patients received capravirine for 28 days. BID, twice daily; TID, 3 times a day.

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retroviral activity was noted at the 20- and 25-mg/kg/day dose levels (figure 1). At the 25-mg/kg/day dose level, the day 15 median (mean) HIV-1 load decreased by 1.34 (1.45) $\log_{10}$ copies/mL (figure 1). Of the 24 patients in the regimen 3 arm with an HIV-1 load >400 copies/mL at study entry, 11 (46%) did not have detectable HIV-1 RNA in plasma on day 29. On days 15 and 29, the mean increase in $CD4^+$ T lymphocyte counts in the patients in the regimen 3 arm was 39 and 51 cells/μL, respectively.

Discussion. The advent of highly active ART has transformed how patients infected with HIV-1 are treated [11–13]. However, toxicity and, increasingly, drug resistance limit the clinical utility of established regimens [14, 15]. In both respects, the second-generation NNRTI capravirine may be an important addition to the current antiretroviral armamentarium, particularly for the rescue of NNRTI-failing regimens.

As predicted on the basis of preclinical animal studies that used significantly higher doses than did the present study, capravirine was well tolerated. No dose-limiting toxicities were observed at the highest daily dose (25 mg/kg/day) tested in this study, the maximum-tolerated dose was not reached, and no capravirine-related rashes were observed. Patterns of adverse events were similar at doses of 8.3 mg/kg every 8 h, 10 mg/kg every 12 h, and 12.5 mg/kg every 12 h. Only 1 possible drug-related adverse event of grade 3 severity or higher was reported, an elevated CK level that returned to normal after cessation of capravirine. Gastrointestinal side effects were minor and may have been partially related to the 25-mg pill size. Of note, capsules as large as 700 mg are now available.

A 2-compartment linear model with α (distribution) and β (elimination) phases best fit the data. Although no significant PK differences were observed between the fasted and nonfasted patients in the regimen 1 arm (the single-dose group), potential food effects may have been masked by intra- and interpatient variability in C_{max} and AUC, as well as by the small sample size. Other studies have determined that gastric pH–altering medications decrease bioavailability, whereas the bioavailability of orally administered capravirine increases by ~85% in the presence of both high- and low-fat food (Pfizer, unpublished data). Although studies have demonstrated the existence of drug-drug interactions between capravirine and P450 CYP3A4 inhibitors, no patients in the regimen 3 arm were concurrently taking PIs.

Capravirine has demonstrated potent antiviral activity in the present NNRTI-naive cohort of patients, many of whom were ART experienced. The median C_{max} and trough values at the 25-mg/kg/day dose level, when administered either 2 or 3 times a day, were well in excess of the IC_{50} and IC_{90} of 1.1 nmol/L (0.5 μg/L) and 3.4 nmol/L (1.5 μg/L), respectively. Single mutations have been shown to confer only partial resistance to capravirine and to increase the EC_{50} only by up to 22-fold in vitro. The capravirine EC_{50} of common NNRTI-resistant variants ranges from 0.3 nmol/L (0.1 μg/L) for K103N to 4.2 nmol/L (1.9 μg/L) for Y181C [8]. Thus, even trough values in the present study were well above the EC_{50} of all common NNRTI-resistant variants. Small reductions in HIV-1 load were observed at daily doses of <20 mg/kg/day, with significant reductions noted at 20 and 25 mg/kg/day. In this heavily pretreated cohort, the members of which were allowed to continue NRTI therapy, a >1.0 $\log_{10}$ reduction (90%) in median HIV-1 load was observed on day 15 in patients receiving 20 or 25 mg/kg/day (figure 1). At the 25-mg/kg/day dose level and after 14 days of treatment, twice- and thrice-daily dosing diminished HIV-1 load to a similar extent (figure 1). On the basis of this result, further clinical trials using twice-daily dosing have begun, to better define the efficacy of capravirine.

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