A Phase I Study of Abacavir (1592U89) Alone and in Combination With Other Antiretroviral Agents in Infants and Children With Human Immunodeficiency Virus Infection

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ABSTRACT. Objectives. To evaluate the pharmacokinetic features, safety, and tolerance of abacavir, given alone and in combination with other nucleoside antiretroviral agents, in symptomatic human immunodeficiency virus (HIV)-infected children.

Methods. HIV-infected children discontinued prior antiretroviral therapy and were given abacavir orally, 4 mg/kg every 12 hours for 6 weeks, followed by 8 mg/kg every 12 hours for 6 weeks (n = 39); or 8 mg/kg every 12 hours for 12 weeks (n = 8). Children then were randomly assigned to receive a second nucleoside antiretroviral agent (zidovudine, stavudine, didanosine, or lamivudine), plus abacavir. Pharmacokinetics, safety, tolerance, CD4+ lymphocyte counts, and plasma HIV RNA concentrations were evaluated.

Results. At a dose of 8 mg/kg every 12 hours, area under the plasma concentration-versus-time curves and plasma half-life values were comparable with those reported for adults receiving abacavir at a dose of 300 mg twice daily. One case each of hypersensitivity reaction and peripheral neuropathy occurred during abacavir monotherapy. Three children experienced neutropenia while receiving abacavir in combination with another antiretroviral agent. Mean CD4+ lymphocyte count and plasma HIV RNA concentration did not change when prior antiretroviral therapy was changed to abacavir monotherapy.


ABBREVIATIONS. HIV, human immunodeficiency virus; ZDV, zidovudine; 3TC, lamivudine; d4T, stavudine; ddI, didanosine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AUC, area under the plasma concentration-versus-time curve; CL/F, apparent oral clearance; SE, standard error; Cmax, maximum observed plasma concentration; T1/2, elimination half-life; MAC, Mycobacterium avium-intracellulare complex.

Abacavir (1592U89) is a carbocyclic 2',3'-ene nucleoside analog that is converted intracellularly to carbovir triphosphate, which acts as an inhibitor of human immunodeficiency virus (HIV) reverse transcriptase. In vitro, resistance to abacavir develops slowly, and laboratory and clinical isolates of HIV with decreased susceptibility to zidovudine (ZDV) are not cross-resistant to abacavir. Additive or synergistic anti-HIV activity has been noted when abacavir is combined with any of several nucleoside antiretroviral agents in vitro.

Early clinical studies of HIV-infected adults indicate that abacavir, given in combination with other nucleoside antiretroviral agents with or without protease inhibitors, generally is well tolerated and safe.
and produces changes in CD4+ lymphocyte counts and plasma HIV RNA concentrations.5–7 Gastrointestinal complaints (abdominal pain, nausea, vomiting); headache; rash; and peripheral neuropathy are the adverse events observed most frequently among abacavir-treated adults.7 Potentially serious hypersensitivity reactions, usually characterized by the presence of fever, nausea, vomiting, malaise, and rash, have been observed in 3% of adults treated with abacavir. In one study, adults without previous antiretroviral therapy were given abacavir alone for 24 weeks, followed by abacavir in combination with ZDV plus lamivudine (3TC) for another 24 weeks.6 Patients experienced a median 24-week decrease in plasma HIV RNA concentration of 1.8 log₁₀ copies/mL during combination therapy, with 56% of patients achieving plasma HIV RNA concentrations <400 copies/mL.

Eighteen HIV-infected infants and children received liquid abacavir, 4 or 8 mg/kg orally, in a phase I single dose study.8 Serious adverse events were not observed. Only two of 100 children treated with abacavir in an ongoing phase III study have manifested suspected hypersensitivity to the drug.9

The present study was designed to evaluate the pharmacokinetic features, safety, and tolerance of multiple doses of abacavir, given alone and in combination with other nucleoside antiretroviral agents in symptomatic, nucleoside antiretroviral therapy-experienced HIV-infected children 3 months to 13 years of age. Data generated from this study have been used to establish doses of abacavir appropriate for pediatric phase II/III clinical trials.

METHODS

Patients and Study Design

The study population included HIV-infected children 3 months to 13 years of age who had received >156 days of antiretroviral treatment at the time of study enrollment. Those children who participated in the phase I single-dose abacavir study also were eligible for enrollment. Laboratory evidence of immunosuppression (Centers for Disease Control and Prevention categories 2 and 3) or symptomatic HIV disease (categories A, B, and C)10 was required for inclusion in the study. The following baseline laboratory values were required: a hemoglobin concentration of >8.7 g/dL; a polymorphonuclear leukocyte count of at least 400/µL; a platelet count of at least 50 000/µL; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <10 times the upper limit of normal; bilirubin <3 times the upper limit of normal; and a serum creatinine concentration <1.2 (age 3 months to 2 years) or 1.7 mg/dL (age 2 to 6 years). Children were excluded from study participation if they had known intolerance to any of the study drugs, were receiving chemotherapy for active malignancy, had an active opportunistic infection, or had intractable or chronic diarrhea or vomiting.

This was an open-label, dose-escalating phase I study conducted in two steps. In step 1, subjects discontinued previous antiretroviral therapy and were given abacavir orally, 4 mg/kg every 12 hours for 6 weeks, followed by 8 mg/kg every 12 hours for 6 weeks (cohort 1); or 8 mg/kg every 12 hours for 12 weeks (cohort 2). In step 2, subjects were randomized to therapy, with a second antiretroviral agent ZDV (AZT), stavudine (d4T), didanosine (ddI), or 3TC, plus abacavir (8 mg/kg every 12 hours). Patients received prophylaxis for Pneumocystis carinii pneumonia according to established guidelines,11 and nutritional support and antibiotic therapy were prescribed as needed. Use of immunomodulators (excluding immunoglobulin) or antiretroviral agents other than the study drugs was prohibited.

Toxicities were graded according to the Division of AIDS Toxicity Grading Table for Pediatric Adverse Experiences. In brief, this Table grades a variety of potential study drug-associated clinical and laboratory adverse events on a 4-point scale from grade 1 (least severe) to grade 4 (most severe). Laboratory values constituting grade 3 or greater abnormalities include the following: hemoglobin concentration, <7 g/dL; absolute neutrophil count, <500/µL; ALT, at least 10 times the upper limit of normal; bilirubin, at least 3 times the upper limit of normal; and serum creatinine, >1.1 (age 3 months to 2 years) or 1.6 mg/dL (age 2 years or older).

Grade 3 or greater instances of toxicity were managed according to a dose modification scheme that mandated interruption of study drug therapy for up to 28 days. If the toxicity improved during that time to less than grade 3, study drug therapy was resumed at full dose.

The primary safety endpoint for this study was defined by the occurrence of any of the following: 1) an apparent study drug-associated grade 4 toxicity; 2) persistence of apparent study drug-associated grade 3 toxicity for 28 days or more after study drug was withheld; 3) recurrence of an apparent study drug-associated grade 3 toxicity; or 4) a life-threatening allergic reaction to the study drug.

If a primary study endpoint was suspected, the investigator was asked to contact the protocol chair. All study endpoints were reviewed by the protocol chair, and only those that satisfied protocol definitions and were not attributable to other causes were included in the analysis.

Drug Administration and Pharmacokinetic Sampling

Abacavir was supplied as abacavir sulfate liquid, 10 mg/mL. It was stored at room temperature. All other study drugs were supplied in standard formulations that are available by prescription. Drug doses were as follows: ZDV, 160 mg/m² (maximum, 200 mg) 3 times daily; d4T, 1 mg/kg (maximum, 40 mg) every 12 hours; ddI 90 mg/m² (maximum, 150 mg) every 12 hours; and 3TC, 4 mg/kg (maximum, 150 mg) every 12 hours. Drugs were stored according to package insert instructions.

Body surface area and weight were determined every 4 weeks, and the drug dose was changed when there was a change of >10%. Compliance was monitored by measuring or counting returned medication and by questioning the parent at each scheduled clinic visit.

Children in cohort 1 reported to the clinic at study weeks 2 and 8 for pharmacokinetic sampling. Blood was collected immediately before the morning dose of the drug, and at 1, 2, 3, and 5 hours after an observed oral dose of abacavir. Children in cohort 2 underwent pharmacokinetic sampling at study entry and week 8. Blood was collected immediately before the morning oral abacavir dose, and at 1/2, 1, 1 1/2, 2, 3, 5, and 6 hours postdose.

Plasma abacavir concentrations were measured by a validated reversed phase high-performance liquid chromatographic method. This assay has a lower limit of quantitation of 25 ng/mL. Interday coefficients of variation at low (50 ng/mL), medium (500 ng/mL), and high (4000 ng/mL) quality control sample concentrations were 9.7%, 3.4%, and 4.3%, respectively, with corresponding average bias values of 0.0%, -0.5%, and 2.4%, respectively.

Abacavir pharmacokinetic parameters were calculated during monotherapy for both cohorts using plasma concentration-time data by noncompartmental methods based on the statistical moment theory.12 Briefly, area under the plasma concentration-versus-time curve (AUC) was calculated by the linear trapezoidal rule (AUCsub). For concentration data obtained after the first dose, AUC from time 0 to infinity (AUC ___) was calculated as AUCsub plus C last/Kel, where C last is the last measured concentration and Kel is the terminal elimination rate constant. When concentration data were collected at weeks 2 and 8, the AUC within the dosing interval was taken as equivalent to AUCsub and was calculated as AUCsub plus C last/Kel minus the predose concentration divided by Kel. Apparent oral clearance (CL/F) was calculated as dose/AUC.

Clinical and Laboratory Monitoring

Subjects were evaluated clinically (physical examination, height, weight, and head circumference for children ≤2 years of age) and with complete blood counts and routine blood chemistries (creatinine, ALT, bilirubin, alkaline phosphatase, and amylase) at screening and entry, and at weeks 2, 6, 8, 12, 14, 16, 20, and...
24 (or end of study). Urinalysis was obtained at entry and at end of study. Immunologic and virologic monitoring included lymphocyte monoclonal antibody phenotyping and plasma HIV RNA measurement by nucleic acid sequence-based amplification (Ory- ganon Technika, Gent, Belgium) at screening and entry, and at weeks 6, 12, 16, and 24 (or end of study).

Statistical Methods

For comparison to on-study weight, CD4+ lymphocyte count, and plasma HIV RNA concentration values, baseline was defined by values obtained immediately before initiation of study treatment. Confidence limits were calculated using exact methods. The statistical significance of each change in value was tested using a two-tailed single sample t test with α = 0.05. Because analyses of response variables were exploratory, no adjustment was made for the number of tests. As a general test that significant results were not attributable to violations of assumptions, all parametric tests were compared with results from the parallel nonparametric tests. In all cases, results were not qualitatively different.

RESULTS

Baseline Patient Characteristics

A total of 47 children were enrolled in the study between February and April 1997 at six separate sites. Selected characteristics of study subjects are shown in Table 1. All children had acquired HIV infection by vertical transmission. Of 47 children, 46 had a history of antiretroviral treatment before study entry, the median duration of which was 3.8 years (range, 0.11 to 7.5 years). The interval between discontinuation of previous antiretroviral therapy and initiation of abacavir was ≤2 days in 42 of 47 children. The mean baseline CD4+ lymphocyte count and plasma HIV RNA concentration were 454 cells/μL (standard error [SE] = 62.7; range, 0 to 1830 cells/μL) and 4.7 log_{10} copies/mL (SE = 0.133; range, 2.6 to 6.4 log_{10} copies/mL), respectively.

Pharmacokinetics

Abacavir pharmacokinetic characteristics are listed in Table 2. The mean (and percent coefficient of variation) AUC for abacavir in children 3 months to 2 years of age (n = 10) was 8.67 μg*h/mL (48%); for children >2 to 6 years of age (n = 15), it was 9.38 μg*h/mL (52%); and for children >6 to 13 years of age (n = 19), it was 10.71 μg*h/mL (43%). Children were evaluated routinely at each clinic visit for adherence with study treatment; however, an effect of less-than-perfect adherence on steady-state pharmacokinetic values cannot be excluded.

Safety

Of 39 children from cohort 1, 37 (4 mg/kg every 12 hours for 6 weeks) followed by 8 mg/kg every 12 hours for 8 weeks) completed monotherapy (step 1) and were randomized to combination therapy with abacavir plus one other antiretroviral agent (step 2). Two children were removed from abacavir monotherapy because of toxicity (1 each of grade 3 hypersensitivity reaction characterized by fever, rash, vomiting, and diarrhea in study week 2; and grade 4 peripheral neuropathy in study week 7). Thus, the rate of treatment-associated toxicity of grade 3 or 4 during abacavir monotherapy among children from cohort 1 was 0.05 (95% confidence limits: 0.01, 0.17). Five other children experienced grade 3 or 4 events that were deemed to be unrelated to study treatment (1 each of increase in serum AST, aphthous ulcers, hyperamylasemia and hyperbilirubinemia, thrombocytopenia, and pneumonia intestinalis).

All 8 children in cohort 2 (abacavir, 8 mg/kg every 12 hours for 12 weeks) completed monotherapy, and none experienced treatment-associated grade 3 or 4 toxicity (rate, 0; 95% confidence limits: 0, 0.37). One child experienced three events unrelated to study treatment (1 each of increase in serum AST, aphthous ulcers, hyperamylasemia and hyperbilirubinemia, thrombocytopenia, and pneumonia intestinalis).

During combination therapy with abacavir and one other antiretroviral agent, three children experienced possible treatment-associated grade 3 or 4 neutropenia (rate, 0.08; 95% confidence limits: 0.02, 0.22). Two of these children were receiving abacavir plus ZDV, and 1 was receiving abacavir plus d4T. Two other children experienced grade 3 or 4 events that were deemed to be unrelated to study treatment (1 case each of thrombocytopenia and rash).

Immunologic, Virologic, and Clinical Observations

There was no change in mean CD4+ lymphocyte count or plasma HIV RNA concentration during abacavir monotherapy. There was a marginally significant increase in percent of age-normalized CD4+ lymphocyte count between baseline and study week 16 (mean, 3.3%; P = .06). There was a significant decrease in plasma HIV RNA concentration between baseline and study week 16 (mean, −0.58 log_{10} cop-
ies/mL; \( P = .0003 \)), and between study week 12, when a second antiretroviral agent was added, and week 16 (mean, \(-0.54 \log_{10} \) copies/mL; \( P = .005 \)).

No acquired immunodeficiency syndrome-defining conditions or deaths were observed during the course of the study. There was no change in mean weight-for-age-and-gender \( z \) score between baseline and study week 6, 12, or 16. There was a significant decrease in weight-for-age-and-gender \( z \) score between baseline and study week 20 (mean [SE], \(-0.16 [0.065]; P = .02 \)).

**DISCUSSION**

The primary objectives of the present study were 1) to assess the steady-state pharmacokinetic features, safety, and tolerance of orally administered abacavir, given alone or in combination with other nucleoside reverse transcriptase inhibitors, in HIV-infected infants and children; and 2) to establish doses of abacavir appropriate for pediatric phase II/III clinical trials. Most of the children studied had advanced HIV disease and a history of lengthy antiretroviral treatment before study enrollment.

The abacavir pharmacokinetic data derived from the present study are in general agreement with data obtained from children receiving only a single dose of abacavir.\(^8\) In that study, average parameter values (and percent coefficient of variation) after a dose of 8 mg/kg were: AUC, 8.09 \( \mu \text{g}\text{ h/mL} \) (37); maximum observed plasma concentration (Cmax), 3.94 \( \mu \text{g/mL} \) (28); elimination half-life (T\( \frac{1}{2} \)), 1.13 hours (21); and CL/F, 18.9 mL/min/kg (41) (\( \sim 1323 \text{ mL/minute} \)). In the single-dose study, the CL/F of abacavir after a dose of 4 mg/kg was 27.4 mL/min/kg (\( \sim 1918 \text{ mL/minute} \)), faster than that observed after a dose of 8 mg/kg and suggestive of dose-dependent pharmacokinetic differences, although no formal statistical comparison was provided. However, the steady-state pharmacokinetic characteristics observed in the present study provide good evidence for dose proportionality between 4 mg/kg and 8 mg/kg, as the AUC and Cmax approximately doubled, and CL/F remained stable. There was no evidence of a first-dose to steady-state change in CL/F in the 8 mg/kg dosing group. In addition, abacavir AUC values at both the 4 mg/kg (data not shown) and the 8 mg/kg doses were similar across the age range, indicating a lack of age-dependency on the pharmacokinetic behavior of the drug.

Among adults receiving an abacavir dose of 300 mg every 12 hours, typical pharmacokinetic characteristics (and percent coefficient of variation) are: AUC, 6.29 \( \mu \text{g}\text{ h/mL} \) (33); Cmax, 2.94 \( \mu \text{g/mL} \) (31); T\( \frac{1}{2} \), 1.22 hours (15); and CL/F, 897 mL/minute (29) (\( \sim 12.8 \text{ mL/min/kg} \)) (J. A. McDowell, manuscript in preparation). The present study demonstrates that children receiving abacavir at a dose of 8 mg/kg every 12 hours have systemic exposures similar to those in adults receiving abacavir at a dose of 300 mg every 12 hours.

Good short-term safety and tolerance were observed in the HIV-infected children we treated with abacavir. One child experienced a serious abacavir-associated hypersensitivity reaction during the course of the study. Hypersensitivity reactions have been observed in \( \sim 3\% \) of adults treated with abacavir (data on file, Glaxo-Wellcome, Inc, Research Triangle Park, NC), usually within 1 to 4 weeks after initiating abacavir therapy. These reactions usually are characterized by the presence of fever, nausea, vomiting, malaise, and rash. Diarrhea, myalgias, and arthralgias also may occur. Abacavir therapy should be discontinued permanently if a hypersensitivity reaction is suspected. A life-threatening reaction can occur with rechallenge.

One of the children treated with abacavir developed severe peripheral neuropathy. This condition, which can occur with HIV disease per se and certain opportunistic illnesses (including *Mycobacterium avium-intracellulare* complex [MAC] infection) or as a consequence of therapy with a variety of antiretroviral and other medications, has not been observed in adults treated with abacavir in two phase III trials, but it has been noted occasionally in adults in association with an abacavir hypersensitivity reaction (data on file, Glaxo-Wellcome, Inc). Our patient, who had disseminated MAC infection and was receiving treatment with a number of medications at the time peripheral neuropathy developed, had only minimal resolution of symptoms after discontinuation of abacavir.

The current study was not designed to evaluate the efficacy of abacavir therapy. However, exploratory analyses of CD4\(^+\) lymphocyte counts and plasma HIV RNA concentrations failed to reveal any meaningful effect of abacavir monotherapy on these markers. Several factors may have contributed to this result, including the absence of a specified washout period for children discontinuing previous antiretroviral therapy and initiating abacavir, and the possibility that extensive prior treatment with other nucleoside reverse transcriptase inhibitors may have selected mutations that limited the efficacy of abacavir. The transient decrease in plasma HIV RNA concentration that was observed at study week 16 probably reflects the addition of a second antiretroviral agent at week 12.

A beneficial effect of therapy on growth was not observed; in fact, a significant decrease in weight growth velocity was observed at study week 20. Weight growth velocity has been shown to be a useful predictor of survival in previous studies of other nucleoside antiretroviral agents in HIV-infected children.\(^{13,14}\)

Based on its consistent and predictable pharmacokinetic properties and good short-term tolerance and safety, abacavir may be a useful agent for inclusion in pediatric HIV combination-therapy regimens. Additional studies will be needed to define better the activity of the drug.

**REFERENCES**


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Pediatrics 1999;103:e47

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