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Clinical Trial of Tolerance of HPA-23 in Patients with Acquired Immune Deficiency Syndrome

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An open-label, multicenter clinical trial assessed the tolerance of HPA-23 (ammonium-21-tungsto-9-antimoniate) in patients with acquired immune deficiency syndrome. Sixty-nine patients were sequentially assigned to receive 0.25, 0.5, 1.0, or 2.0 mg of HPA-23 per kg intravenously 5 days per week for 8 weeks. HPA-23 was fairly well tolerated at doses of 1.0 mg/kg or less; nearly 60% of patients given 2.0 mg/kg discontinued treatment. Twenty-six patients discontinued treatment because of adverse events or concurrent illness. HPA-23 produced dose-related decreases in platelet count and increases in serum glutamine oxalacetic transaminase. There were no changes in immune system function, as determined by total lymphocyte count, T_4-cell count, T_8-cell count, and T_4/T_8 ratio. The effects of HPA-23 seemed to be more closely related to the total dose than to the daily dose. No improvement in the clinical status of the patients was observed during the 8 weeks of treatment.

Acquired immune deficiency syndrome (AIDS) is caused by a retrovirus, human immunodeficiency virus type 1 (HIV-1) (2, 6, 11, 13). HPA-23 (ammonium-21-tungsto-9-antimoniate) inhibits retrovirus replication by inhibiting RNA-dependent DNA polymerases and thus could be effective in the treatment of HIV-1 infections and AIDS. HPA-23 inhibits nucleic acid polymerases in vitro (1, 4, 7, 10) and has antiviral activity both in vitro (14) and in vivo (8, 9). Furthermore, HPA-23 inhibits HIV-1 reverse transcriptase in vitro (5). Preliminary observations in a limited number of AIDS patients suggest that HPA-23 inhibits HIV-1 replication (12). The goal of this study was to assess the tolerance of patients with AIDS to HPA-23.

(Portions of this study were presented at the Third International Conference on Acquired Immunodeficiency Syndrome, 1–5 June 1987, Washington, D.C.)

MATERIALS AND METHODS

This was an open-label, multicenter clinical trial. The Institutional Review Board at each institution approved the study protocol, and all patients gave informed consent. Patients were assigned nonrandomly to the treatment groups, and no placebo was used. Initially, a group of patients was treated with the lowest dose of HPA-23 (0.25 mg/kg per day), and the preliminary data on adverse events in these patients were evaluated. After evaluation of the results from this group, additional groups of patients were treated with higher doses of HPA-23.

Patients who had AIDS, as defined by the Centers for Disease Control (Atlanta, Ga.), and who were between 18 and 60 years old, clinically stable, and ambulatory were eligible for this clinical trial. Excluded were females of childbearing potential; patients who had hemophilia; lymphoma; visceral Kaposi's sarcoma (KS); neutropenia (leukocyte count, $<1{,}000/mm^3$); thrombocytopenia (platelet count, $<100{,}000/mm^3$); prolonged coagulation times (prothrombin time or partial thromboplastin time of more than 2 or 8 s longer than the control times, respectively); elevated serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase, or alkaline phosphatase (greater than 2 times the upper normal limit for the laboratory of each investigator) or bilirubin (above the upper limit of the normal range); or those who had received biological response modifiers, cytotoxic chemotherapy, other investigational drugs, or radiation therapy during the 4 weeks before the beginning of treatment or who had received medications other than mild sedatives or acetaminophen during the 7 days before treatment.

During treatment, patients received a daily intravenous infusion of 0.25, 0.5, 1.0, or 2.0 mg of HPA-23 per kg 5 days per week for 8 weeks. Each infusion lasted 5 min, and no dosage adjustments were allowed. Treatment was discontinued if an illness requiring systemic medication developed; if a serious adverse event occurred; or if results from hematology, clinical chemistry, or urinalysis tests exceeded predefined limits. Only topical antifungal drugs, mild sedatives, and acetaminophen were allowed during HPA-23 treatment.

Before treatment, weekly during treatment, and within 72 h following treatment, a physical examination was performed, blood was collected for hematology and clinical chemistry tests, and urine was collected for urinalysis. The occurrence of clinical symptoms of AIDS (fevers, night sweats, fatigue, diarrhea, and weight loss) was noted. Blood was collected before and within 72 h after treatment to measure lymphocyte subsets.

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TABLE 1. Patient population, duration of treatment, dose, and reasons for discontinuing treatment[a]

HPA-23 dose (mg/kg)	No. of patients	Age (yr)	Wt (kg)	No. of patients with the following presenting manifestations:			All patients		Patients who discontinued treatment		No. of patients with the following reasons for discontinuing treatment:		
				KS	OI[b]	KS and OI	Treatment duration (days)[c]	Total dose (mg/kg)	Treatment duration (days)[c]	Total dose (mg/kg)	Clin adv event[d]	Abnormal test result	Concurrent illness
0.25	16	37.4 ± 6.2	68.2 ± 10.6	8	6	2	56 (22–56)	8.9 ± 2.0	40 (22–50)	6.8 ± 1.9	0	1[e]	5
0.5	16	38.7 ± 6.5	70.2 ± 8.3	3	10	3	56 (21–56)	18.5 ± 3.6	39 (19–47)	13.5 ± 4.6	1	0	3
1.0	23	39.5 ± 7.1	72.0 ± 8.0	7	13	3	56 (21–56)	39.9 ± 7.7	38 (19–52)	26.4 ± 8.2	0	3[f]	4
2.0	14	36.9 ± 7.9	74.9 ± 11.0	9	3	2	29 (7–56)	48.4 ± 28.0	16 (5–46)	30.9 ± 17.8	5	3[g]	1

[a] Data are means ± standard deviations or numbers of patients, except where otherwise indicated. All patients were male.
[b] OI, Opportunistic infection.
[c] Median (range).
[d] Clinical adverse event.
[e] 4+ proteinuria.
[f] Protocol-defined thrombocytopenia (platelet count, <40,000/mm^3) for two patients and platelet count of 46,000/mm^3 for one patient.
[g] Protocol-defined thrombocytopenia for two patients and platelet count of 55,000/mm^3 for one patient.

The data were analyzed by analysis of variance (ANOVA), analysis of covariance, and logistic regression.

RESULTS

Table 1 characterizes the patient population and treatment. All patients were males. Comparison of the pretreatment values among the groups showed that there were no significant differences in age, but patients given 2.0 mg of HPA-23 per kg weighed more and that group contained relatively more patients with KS and fewer with opportunistic infections.

Patients given 2.0 mg of HPA-23 per kg had higher pretreatment T_4-cell counts and T_4/T_8 cell ratios compared with the patients in the other treatment groups (Table 2).

Six patients discontinued treatment because of adverse clinical events: one patient given 0.5 mg of HPA-23 per kg developed a generalized rash; five patients given 2.0 mg of HPA-23 per kg had headaches, fever and vomiting, cellulitis, phlebitis at the infusion site, or lymphangitis and anemia. Seven patients discontinued treatment because of abnormal laboratory test results: One patient given 0.5 mg of HPA-23 per kg had proteinuria, two patients each in the groups given 1.0 and 2.0 mg of HPA-23 per kg had protocol-defined thrombocytopenia (platelet count, <40,000/mm^3), and one patient each given 1.0 and 2.0 mg of HPA-23 per kg discon-

TABLE 2. Lymphocyte counts in AIDS patients treated with HPA-23[a]

HPA-23 dose (mg/kg), time, and significance	No. of patients	No. of observations	Lymphocyte count (cells/ml [10^3])	T_4-cell count (cells/ml)	T_8-cell count (cells/ml)	T_4/T_8 ratio
0.25	16					
Before treatment		16	823	88	452	0.19
Posttreatment (72 h)		14	767	70	389	0.18
0.5	16					
Before treatment		16	682	43	343	0.13
Posttreatment (72 h)		11	903	59	497	0.12
1.0	23					
Before treatment		23	976	96	505	0.19
Posttreatment (72 h)		21	812	53	410	0.13
2.0	14					
Before treatment		14	1,090	183	542	0.34
Posttreatment (72 h)		9	1,080	103	595	0.17
Significance level (P) for:						
Groups[b]						
Before treatment			NS[c]	<0.04	NS	<0.10
Posttreatment (72 h)			NS	NS	NS	NS
Treatment[d]			NS	<0.07	NS	NS

[a] Data are medians for all variables.
[b] For comparison among treatment groups (ANOVA); analysis of log-transformed data for all data.
[c] NS, Not significant.
[d] For difference between pre- and posttreatment values or proportional change (ANOVA); analysis of log-transformed data for all data.

TABLE 3. Platelet count and SGOT in AIDS patients treated with HPA-23

HPA-23 dose (mg/kg), time, and significance	No. of patients	No. of observations	Platelet count (cells/ml [10^3])[a]	SGOT (IU/ml)[a]
0.25	16			
Before treatment		16	206 ± 60	28
End of treatment		16	186 ± 68	37
0.5	16			
Before treatment		16	213 ± 63	32
End of treatment		16	147 ± 66	44
1.0	23			
Before treatment		23	221 ± 56	29
End of treatment		23	110 ± 85	49
2.0	14			
Before treatment		14	176 ± 40	29
End of treatment		13	78 ± 46	51
Significance level				
Groups[b]				
Before treatment			NS[c]	NS
End of treatment			<0.0006	<0.07
Treatment[d]			<0.0001	<0.07

[a] Data are means ± standard deviations for platelet count and median for SGOT.
[b] For comparison among treatment groups (ANOVA); analysis of log-transformed data for SGOT.
[c] NS, Not significant.
[d] For difference between pre- and posttreatment values or proportional change (ANOVA); analysis of log-transformed data for SGOT.

tinued treatment because of thrombocytopenia (platelet counts, 46,000 and 55,000/mm^3, respectively), even though the platelet counts remained above the protocol-defined limit. Thirteen patients discontinued treatment because of concurrent illnesses that required systemic therapy: eight for verified opportunistic infections (*Pneumocystis carinii* pneumonia, mycobacterial infection, candidal esophagitis, or cryptosporidiosis) and five for presumed, although unverified, *P. carinii* pneumonia.

Tolerance of HPA-23. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) were reported by 23 of 69 patients (33.3%). Eight patients (11.6%) had bleeding episodes (nosebleeds or gingival or rectal bleeding); four of these patients had mild to moderate abnormalities in their platelet count, prothrombin time, and/or partial thromboplastin time. Adverse events related to the central nervous system, commonly, amnesia, dizziness, and paresthesias, were reported by seven patients (10.1%). Also, fever and/or chills (13.0%), headache (7.2%), phlebitis at the infusion site (2.9%), and generalized rash (2.9%) were reported.

Table 3 summarizes the effects of HPA-23 on platelet count and SGOT. Statistical comparison of the pretreatment values showed no statistically significant differences among the groups. For platelet count, the change caused by HPA-23 was calculated as the difference between posttreatment and pretreatment values, and for SGOT the change was calculated as the ratio of the posttreatment to pretreatment values; these changes were analyzed by ANOVA. HPA-23 produced a dose-related decrease in platelet count ($P < 0.0001$) and an increase in SGOT ($0.05 < P < 0.07$). For both platelet count and SGOT, analysis of covariance showed a significant relationship ($P < 0.001$) with the interaction of treatment group and duration of therapy, suggesting that the effects were related to the total dose of HPA-23. Changes in serum glutamic pyruvic transaminase were similar to those for SGOT.

Six patients discontinued treatment because of thrombocytopenia. To determine recovery, the platelet counts for five of these patients were measured after the end of treatment; the duration of follow-up ranged from 3 to 28 days. At the last observation, all five patients had platelet counts higher than 50,000/mm^3, and two had platelet counts higher than 100,000/mm^3.

Although the effect of HPA-23 on SGOT activity was related to dose and was statistically significant, the effect was considered to be not clinically significant. HPA-23 treatment also produced a significant decrease in granulocyte count. There were no dose-related changes in other clinical chemistry and hematology test values attributed to HPA-23 treatment.

No patient died during treatment. One patient given 0.25 mg of HPA-23 per kg died from *P. carinii* pneumonia within 2 weeks after treatment; this death was considered unrelated to treatment.

Effects of T lymphocytes. Table 2 summarizes the effects of HPA-23 on T lymphocytes. Statistical analysis of the pretreatment values showed no significant differences among the groups in lymphocyte count, T_8-cell count, or T_4/T_8 ratio; but the T_4-cell count was higher in the group given 2.0 mg of HPA-23 per kg than in the other groups. Comparison of pretreatment and posttreatment values showed no significant differences in lymphocyte count, T_8-cell count, or T_4/T_8 ratio; but the T_4-cell count was significantly decreased in the posttreatment observation.

Clinical status. Treatment with HPA-23 did not appear to reduce the occurrence of new opportunistic infections or produce any significant improvement in KS, lymphadenopathy, clinical symptoms, or body weight. No newly recognized cases of KS developed during treatment among patients who did not have KS at the base line.

DISCUSSION

The results of this study demonstrate that daily doses of 1.0 mg of HPA-23 per kg or less are reasonably well tolerated by patients with AIDS. Gastrointestinal symptoms were the most frequently observed adverse events; other adverse events were central nervous system effects, headaches, fever and/or chills, vomiting, phlebitis, and generalized rash. HPA-23 produced reversible thrombocytopenia and mild elevation of SGOT; these effects were more closely related to the total dose of HPA-23 than to the daily dose. Thrombocytopenia was the most frequent cause of dose discontinuation.

The observation that the effects of HPA-23 were more closely related to the total dose than to the daily dose is important. Results of clinical pharmacokinetics studies have indicated that HPA-23 is sequestered in tissues (D. M. Kornhauser, B. G. Petty, D. W. Chan, D. A. Druckman, B. F. Polk, C. R. Smith, and P. S. Lietman, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1098, 1986), which may explain why the effects in our study were related to the total dose. A more appropriate dosing regimen may be to give a large loading dose of HPA-23 followed by smaller doses to maintain adequate concentrations of HPA-23 in tissues, provided that such a loading dose would not cause irreversible toxicity.

HPA-23 produced no significant improvement in T-lymphocyte counts or in the clinical symptoms of AIDS. Such

absence of clinical effect is not surprising since the maximum observation period was only 8 weeks and this study was not designed to evaluate the efficacy of HPA-23. P_{24} antigen levels in our patients were not determined. Although reverse transcriptase activity assays to measure the presence of HIV-1 were performed, the methodology varied among the centers and a central laboratory. Reverse transcriptase activity values often differed significantly when a single specimen was analyzed at more than one laboratory. As a result, and because the objective of this study was to assess the tolerance of HPA-23, an overall analysis of the antiviral activity of HPA-23 was not conducted. Nonetheless, investigators at one center have concluded from their data that HPA-23 at daily doses of 0.5 or 1.0 mg/kg reduced HIV-1-specific reverse transcriptase activity during treatment (3).

Further interpretation of these results is limited by the experimental design: There was no control group and patients were assigned to treatment groups nonrandomly. Further pharmacokinetics studies are needed to develop rational dosing regimens. In future studies, platelet count and SGOT should be monitored to evaluate HPA-23 toxicity.

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