



5/9/1  
00613446

## EL-10 IND for AIDS Granted

Antiviral Agents Bulletin December 00, 1988 V. 1 NO. 9

WORD COUNT: 192

PUBLISHER: OMEC International, Inc.

EL-10, an antiviral from Elan (Eire, UK) has been granted IND status by FDA, allowing for initiation of U.S. clinical trials. E copolymer adsorbate of dihydroepiandrosterone (DHEA) base which has antiviral effects in HIV-infected cells, including macrophages. In studies, EL-10 has also shown immune stimulating effects. Elan has exclusive licensing rights to EL-10 which it acquired from Colthur (UK).

A Phase II study involving 16 EL-10 and 8 placebo-receiving AIDS patients is already in progress at the Academic Medical Centre (Amsterdam, Netherlands). A Preclinical New Drug Submission has been filed with Canadian authorities for initiation of clinical testing at two sites under different protocols in Canada.

Safety and efficacy studies in early AIDS patients, including oral administration, will begin shortly in San Francisco, CA. Patients receive EL-10 orally. Initial trials are concentrating on subjects with laboratory and clinical profiles indicating potential for early progression to more advanced HIV-infection, such as full AIDS. Later studies will investigate possible prophylactic uses of EL-10 in healthy HIV-positive persons. Multicenter studies are planned for early 1989.

Elan has exclusive licensing rights to EL-10 for treatments for HIV-infection obtained from Dr. P. Prendergast, Colthurst Ltd.

COPYRIGHT 1988 by OMEC International, Inc.

Subscription: \$275 per year as of 9/88. Published monthly. Contact OMEC International, Inc., 727 Fifteenth Street NW, Washington, DC 20005. Phone (202) 639-8900. FAX (202) 639-8993.

INDUSTRY: Medical and Health (MH)

IAC Newsletter DB(TM) (Dialog® File 636): (c) 1998 Information Access Co. All rights reserved.

© 1998 The Dialog Corporation plc

5/9/1

00181846 Word Count: 359

## Two AIDS therapies granted US investigational new drug (IND)s

Story Type: F

Scrip 1367 p20 Publication Date: 881207

Two potential AIDS therapies, Elan's oral antiviral, EL-10, and Carrington Laboratories' immunomodulator, Carrisyn, have recently been granted US INDs.

EL-10, a copolymer absorbate of dehydroepiandrosterone (DHEA) base, has been shown to exert an antiviral effect in vitro in HIV-infected human cells, and it has also shown immunological properties and evidence of protection against lethal non-HIV viral challenge in animal studies, according to Elan. The first US clinical study with the drug, which will begin in San Francisco soon, will evaluate the drug's safety and efficacy at different dose levels in HIV-seropositive individuals.

Following encouraging results in a small French study involving 12 patients, a placebo-controlled trial of EL-10 is already underway in Amsterdam, the Netherlands, and a preclinical new drug submission has been filed in Canada with a view to initiating two multicentre studies with different protocols early in 1989.

Initial trials in the US and elsewhere will involve HIV-seropositive asymptomatic or early ARC patients whose laboratory and clinical parameters reflect the potential for early progression to more serious illness. Later, longer-term studies will investigate a possible prophylactic role for EL-10 in healthy HIV-positive individuals, the company told Scrip.

Elan of Athlone, Ireland, has exclusive worldwide rights, licensed from microbiologist Patrick Prendergast and his company, Colthurst Ltd, which is based outside Dublin, to develop, manufacture, market and sub-license EL-10 and related compounds for the systemic treatment of HIV infection and its complications.

Carrisyn

Carrington Laboratories' immunomodulator, Carrisyn (acemannan), has been approved for a clinical trial to evaluate several dosage levels of the orally administered drug in 24 healthy volunteers. The study is expected to take approximately eight weeks, with a final report due in four months. Clinical trials with Carrisyn are already underway in Belgium, where the drug is being tested in AIDS patients (see Scrip No 1323, p 25).

The US study will evaluate the effects of Carrisyn on the immune system, and should prove to be valuable in the interpretation of the Belgian results, Carrington commented. Also, the information provided by the US study may serve as a basis for future studies of the efficacy of Carrisyn in the treatment of specific human diseases, the company added.

PHIND(Archival) (Dialog® File 129): (c) 1998 PJB Publications, Ltd. All rights reserved.

© 1998 The Dialog Corporation plc

## An Open-Label Dose-Escalation Trial of Oral Dehydroepiandrosterone Tolerance and Pharmacokinetics in Patients with HIV Disease

Toby S. Dýner, William Lang, Jaime Geaga, \*Allyn Golub, †Daniel Stites, ‡Edward Winger, §Mirta Galmarini, ¶Joe Masterson, and ¶Mark A. Jacobson

California Pacific Medical Center, California Campus, \*Guidelines, Inc., Miami, Florida, †Department of Laboratory Medicine, University of California, San Francisco, ‡Immunodiagnostic Laboratories, San Leandro, California, §Hols Institute, San Juan Capistrano, California, ¶Elan Pharmaceuticals, Athelone, Ireland, ¶Department of Medicine, University of California, San Francisco and the Medical Service, San Francisco General Hospital, San Francisco, California, U.S.A.

**Summary:** Dehydroepiandrosterone (DHEA) is a naturally occurring adrenal steroid reported to have immunomodulatory and antiviral activity in cellular and animal models as well as modest in vitro antiretroviral activity against human immunodeficiency virus (HIV). A phase I dose-escalation study was performed to evaluate the safety and pharmacokinetics of DHEA in subjects with symptomatic HIV disease and an absolute CD4 lymphocyte count between 250 and 600 cells/ $\mu$ l. Thirty-one subjects were evaluated and monitored for safety and tolerance. The oral drug was administered three times daily in doses ranging from 750 mg/day to 2,250 mg/day for 16 weeks. Some immunological and virological parameters were monitored as well. The drug was well tolerated and no dose-limiting side effects were noted. Dose proportionality was evidenced neither by the serum DHEA nor by DHEA-S time-concentration curves for the three dosing groups. However, the study cohort appeared to consist of two subpopulations with markedly different bioavailability for a given DHEA dose. No sustained improvements in CD4 counts nor decreases in serum p24 antigen or  $\beta$ -2 microglobulin levels were observed. However, serum neopterin levels decreased transiently by 23–40% at week 8 compared with baseline in all dosing groups. DHEA was well tolerated by patients with mild symptomatic HIV disease; evaluation of this agent for efficacy in HIV disease would require randomized, controlled trials. **Key Words:** DHEA—HIV—Open label trial—Dose escalation trial.

Dehydroepiandrosterone (DHEA) is an abundant naturally occurring adrenal steroid. In blood, it is found mainly as the sulfate derivative, DHEA-S. In humans, serum DHEA and DHEA-S levels are low early in life, rise to a peak at approximately age 30

years, and then decline with age. Although the metabolic properties of this endogenous steroid are well delineated, its biologic function is poorly understood. Animal studies have suggested a role for DHEA as an anticarcinogen (1) and in providing protection against lethal viral infections (2). Recent reports also suggest that DHEA is a potent enhancer of interleukin-2 production by activated T cells (3) and has some modest direct antiretroviral activity in human immunodeficiency virus (HIV)-infected lymphocytes and macrophages (4).

Address correspondence and reprint requests to Dr. M. Jacobson at Ward 84, Building 80, 995 Potrero Ave, San Francisco, CA 94110, U.S.A.  
Manuscript received May 20, 1992; accepted November 13, 1992.

Epidemiologic observations of plasma DHEA and DHEA-S levels in HIV infection have noted decreased levels in patients with HIV disease compared with age-matched HIV-seronegative controls (5), with a trend toward greater decreases in advanced HIV disease (5,6). The relationship between serum DHEA and DHEA-S levels and subsequent progression to AIDS has been investigated independently in two large HIV natural history cohort studies (7,8). Both of these studies reported low serum DHEA levels to be an independent predictor of risk of subsequent progression to AIDS.

Prior clinical studies in patients without HIV disease have reported that DHEA oral doses of up to 1,600 mg per day have been well tolerated, with minimal side effects (9-12). We now report on a phase I dose-escalation study of DHEA tolerance and pharmacokinetics in patients with mild symptomatic HIV disease and absolute CD4 lymphocyte counts between 250 and 600 cells/ $\mu$ l.

## METHODS

### Subject Population

Men >18 years of age, with documented HIV-1 seropositivity and mild symptomatic HIV disease, were eligible to enroll in the study. Mild symptomatic HIV disease was defined as any one of the following: unintentional weight loss, unexplained fevers, drenching night sweats, unexplained diarrhea, neurological abnormalities (including peripheral neuropathy, myelopathy, or cognitive deficits), oral hairy leukoplakia, oral candidiasis, herpes zoster within 2 years before study entry, unexplained anemia with a hemoglobin of <13.5 g/dl, or unexplained neutropenia with an absolute neutrophil count <1,500 cells/ $\mu$ l. Subjects were required to have an absolute CD4 lymphocyte count between 250 and 600 cells/ $\mu$ l and a Karnofsky performance score >60. No other antiretroviral or immunomodulating drugs were allowed within 60 days before study entry nor during the study period. Patients with a history of an AIDS-defining opportunistic infection or neoplasm or underlying medical illness requiring treatment with systemic corticosteroid drugs were excluded. Subjects were enrolled between April 1989 and September 1990. After zidovudine approval was extended in March 1990 by the U.S. Food and Drug Administration to treatment of HIV disease in patients with absolute CD4 lymphocyte counts <500 cells/ $\mu$ l, subjects were informed of zidovudine availability and were given the option of not enrolling or discontinuing study medication to initiate zidovudine. Informed consent was obtained from all subjects. All procedures conformed to the guidelines established by the U.S. Department of Health and Human Services and the University of California, San Francisco, for conduct of clinical research.

### DHEA Dosage Regimen

DHEA was administered as a powder, mixed in water or juice, and taken by mouth three times daily. Dosage levels studied were 250, 500, and 750 mg t.i.d. Dose assignment was open label,

nonrandomized, and sequential. Enrollment for the subsequent dose level began after all patients at a lower dose had completed at least 8 weeks of the 16-week study period.

### Clinical and Laboratory Evaluation and Subject Management

Baseline pretreatment evaluations included complete history and physical examination, HIV serostatus determination, complete blood count with differential, prothrombin time, partial thromboplastin time, serum chemistries, liver function tests, G6PD level, urinalysis, serum hormone studies [DHEA, DHEA-S, testosterone, luteinizing hormone, follicle-stimulating hormone, baseline cortisol, and 60-min cortisol after Cosyntropin (Cortrosyn; Organon; Oss, Netherlands) stimulation], serum p24 antigen, serum  $\beta$ -2 microglobulin, serum neopterin, absolute peripheral lymphocyte counts (CD3, CD4, and CD8), lymphocyte function assays (including phytohemagglutinin and cytomegalovirus antigen stimulation and mixed lymphocyte culture), and skin test reactivity to tetanus, streptococcus, candida, trichophyton, proteus, tuberculin, and diphtheria antigens. Patients were evaluated every 2 weeks for 16 weeks with history and physical examination, complete blood count, serum chemistries, prothrombin time, partial thromboplastin time, and urinalysis performed. Hormonal, virologic, and immunologic studies also were repeated at weeks 8 and 16.

Given that the primary objective of this trial was to evaluate the safety of administering three oral DHEA dosing regimens, the primary study endpoint was subject withdrawal due to drug toxicity. Using standard National Institute of Allergy and Infectious Diseases toxicity grading, subjects were withdrawn from the trial if any grade 2 or greater toxicity developed when the patient's baseline value was grade 0, if any grade 3 or 4 toxicity developed when the baseline was grade 1, or if any grade 4 toxicity developed when the baseline was grade 2. Patients were also withdrawn if their absolute CD4 lymphocyte count dropped below 200 cells/ $\mu$ l.

### Pharmacokinetic Evaluation

Five subjects from each dosing group had 24-h urine collection obtained for 17-ketosteroid measurement simultaneous with blood samples obtained for DHEA and DHEA-S measurement at study entry and once during the 2nd week of dosing immediately before and 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, and 8 h after study drug dosing. Serum levels of DHEA and DHEA-S were measured by methods previously described (7).

## RESULTS

A total of 54 patients were screened, of whom 31 were enrolled in the study. Of these, six, who were entered at the 250-mg dose, were administered mixed doses due to a pharmacy dispensing error. Because the actual dose received was unknown, they were considered unevaluable for analysis of immunologic and virologic effects.

Of the remaining 25 patients, 8 were assigned to 750 mg/day, 7 to 1,500 mg/day, and 10 to 2,250 mg/

day. Two patients in the 1,500 mg/day group did not return after the first visit and were excluded from analysis of clinical, immunologic, and virologic effects. All patients who received drug are included in the safety analysis.

Of the 31 patients who received DHEA, 23 completed 16 or more weeks of DHEA therapy. Five voluntarily withdrew after 0-4 weeks on study, ostensibly to enroll in other studies, and 3 withdrew after 10-14 weeks to begin zidovudine therapy because of absolute CD4 lymphocyte decline <200 cells/ $\mu$ l. All patients were homosexual and all but one were white. Hairy leukoplakia and thrush were the most frequent prior HIV-associated conditions (Table 1). Baseline characteristics of the 25 patients who received known doses of study drug are summarized in Table 1. There was a statistically significant difference in age between the groups: Participants in the 1,500 mg/day group were older ( $p = 0.025$ ). There were no other significant differences in baseline characteristics between groups.

Toxicity

None of the study participants had serious or dose-limiting toxicity. One patient had mild headaches (dose unknown) and one had mild insomnia (dose 2,250 mg/day) that resolved off study drug, occurred with rechallenge, and appeared likely to be related to study drug exposure. All patients de-

veloped some new, mild, symptomatic adverse experiences or mild, objective adverse events during the study, which possibly may have been related to DHEA exposure, HIV disease, or other concurrent medical conditions; these are summarized in Table 2. No consistent or significant dose-related pattern in these adverse events was observed. However, a trend toward increased nasal congestion and fatigue at the highest dose was observed. Analysis of concomitant medications revealed no evidence of adverse drug interactions (data not shown).

As an additional assessment for potential DHEA-induced toxicity, all vital signs and laboratory parameters measured at weeks 8 and 16 were compared with baseline values. Hemoglobin and red blood cell counts decreased slightly (<10%) between baseline and week 16 in all dose groups.

Clinical, Virologic, and Immunologic Changes Associated with DHEA Therapy

There was a trend toward less CD4<sup>+</sup> decline over the course of the study among patients receiving the higher doses as compared with the lowest dose (Table 3). At week 8, absolute CD4 count had decreased by a mean 53 cells/ $\mu$ l in the 750 mg/day group and increased by a mean 8 cells/ $\mu$ l in the two combined higher doses, a difference of 61 cells/ $\mu$ l [95% confidence interval (CI) 114, 7;  $p = 0.03$  t test]. At week 16, the difference in mean CD4 cell

TABLE 1. Baseline characteristics of patients receiving oral dehydroepiandrosterone: median (range) values or proportion of patients with characteristic

	Daily dose		
	750 mg	1,500 mg	2,250 mg
Age (yrs)	39.7 (27.9-45.4)	45.6 (38.8-48.6)	34.8 (25.1-49.7)
Weight (lb)	158.5 (140.0-194.0)	154.0 (145.0-188.0)	165.3 (138.0-180.0)
CD4 (cell/ $\mu$ l)	445.0 (266.0-528.0)	375.0 (336.0-532.0)	385.0 (299.0-540.0)
Hgb (g/dl)	14.6 (13.5-16.2)	15.3 (12.7-16.9)	14.6 (11.8-16.1)
WBC (cells/ $\mu$ l)	4.4 (3.8-6.9)	4.8 (3.6-13.2)	4.8 (3.0-5.4)
Cr (mg/dl)	1.1 (0.7-1.2)	0.9 (0.8-1.3)	1.1 (1.0-1.2)
ALT (IU/L)	43.0 (15.0-100.0)	63.0 (56.0-71.0)	21.0 (11.0-57.0)
Karnofsky score = 90	1/8	2/7	7/10
Karnofsky score = 100	7/8	5/7	3/10
Ever used tobacco	3/8	5/7	7/10
Hairy leukoplakia	2/8	6/7	7/10
Thrush	4/8	0/7	6/10
Zoster	1/8	0/7	1/10
Diarrhea	1/8	0/7	1/10
Anemia	0/8	0/7	0/10
Night sweats	0/8	1/7	1/10
Weight loss	0/8	1/7	0/10

CD4, absolute CD4 lymphocyte count; Hgb, hemoglobin; WBC, white blood cell count; Cr, serum creatinine; ALT, alanine aminotransferase.

TABLE 2. Mild adverse events possibly related to dehydroepiandrosterone exposure

Adverse event	% of all participants	Dose			
		750 mg (N = 8) (%)	1,500 mg (N = 7) (%)	2,250 mg (N = 10) (%)	Unknown (N = 6) (%)
Nasal congestion	39	1/8 (13)	3/7 (43)	7/10 (70)	1/6 (17)
Headache	35	5/8 (63)	0/7 (0)	4/10 (40)	2/6 (33)
Fatigue	29	2/8 (25)	1/7 (14)	5/10 (50)	1/6 (17)
Nausea	26	1/8 (13)	3/7 (43)	3/10 (30)	1/6 (17)
Abnormal ALT	23	3/8 (38)	1/7 (14)	3/10 (30)	0/6 (0)
Cough	23	3/8 (38)	1/7 (14)	2/10 (20)	1/6 (17)
Fevers	19	3/8 (38)	1/7 (14)	1/10 (10)	1/6 (17)
Arthralgias	19	1/8 (13)	1/7 (14)	2/10 (20)	2/6 (33)
Insomnia	19	3/8 (38)	1/7 (14)	2/10 (20)	0/6 (0)
Rash	16	1/8 (13)	2/7 (29)	1/10 (10)	1/6 (17)
Diarrhea	16	1/8 (13)	0/7 (0)	2/10 (20)	2/6 (33)
Polyuria	13	0/8 (0)	0/7 (0)	1/10 (10)	3/6 (50)
Neutropenia	13	1/8 (13)	1/7 (14)	2/10 (20)	0/6 (0)
Hyperglycemia	10	0/8 (0)	1/7 (14)	2/10 (20)	1/6 (17)

ALT, alanine aminotransferase.

change between the lowest and two higher dose groups was 72 cells/ $\mu$ l (95% CI 151, -7;  $p = 0.07$ ). Neopterin declined transiently at week 8 at all dose levels studied by 23-40% compared with baseline values. This decline was marginally significant for the highest DHEA dose (Table 3). Also, 4 of 10 patients who received the highest DHEA dose had a significant improvement in lymphocyte response to cytomegalovirus (CMV) antigen at week 8 compared with baseline versus 0 of 15 who received lower doses ( $p = 0.02$ , Fisher exact test, data not shown). There were no consistent changes in weight, Karnofsky score, absolute CD8 cells, percentage of CD4 lymphocytes, p24 antigen, or  $\beta_2$ -microglobulin (data not shown). There was no trend toward increased or decreased delayed-type hypersensitivity or lymphocyte function as measured by skin test reactivity or other lymphocyte function assays.

#### Pharmacokinetics

Baseline serum DHEA, DHEA-S, and urinary 17-ketosteroid values were obtained on entry, and were comparable for the three dosing groups. Baseline serum DHEA values (ng/ml  $\pm$  SD) were  $5.27 \pm 5.07$ ,  $2.27 \pm 0.98$ , and  $3.41 \pm 3.09$  for the 750, 1,500, and 2,250-mg dosing groups, respectively. Baseline serum DHEA-S levels ( $\mu$ g/ml  $\pm$  SD) were  $2.86 \pm 1.62$ ,  $1.44 \pm 0.65$ , and  $1.64 \pm 0.34$ , and baseline 24-h urinary 17-ketosteroids (mg/day  $\pm$  SD) were  $10.4 \pm 1.82$ ,  $12.8 \pm 1.92$ , and  $13.8 \pm 3.49$  for the three groups. Serum DHEA and DHEA-S time-concentration curves obtained during the 2nd week of DHEA therapy showed good general agreement between the 0 and 8-h trough, supporting the steady-state character of these serum time-concentration curves (Figs. 1 and 2). During DHEA therapy, trough serum DHEA and DHEA-S con-

TABLE 3. Baseline values and subsequent changes compared with baseline in serum neopterin and absolute CD4 lymphocytes associated with dehydroepiandrosterone therapy

	Median (n)			p value*		
	750 mg	1,500 mg	2,250 mg	750 mg	1,500 mg	2,250 mg
CD4 count (cells/ $\mu$ l)						
Baseline	445 (8)	375 (5)	385 (10)			
Week 8 change	-78 (8)	39 (5)	4 (10)	0.05	0.35	0.96
Week 16 change	-126 (6)	42 (4)	-5 (10)	0.03	0.72	0.72
Neopterin (nmol/L)						
Baseline	13.60 (8)	-9.00 (5)	13.20 (10)			
Week 8 change	-5.45 (8)	-2.10 (5)	-3.80 (10)	0.07	0.89	0.04
Week 16 change	-1.45 (6)	5.95 (4)	-3.45 (10)	0.60	0.07	0.09

\* Kruskal-Wallis test.

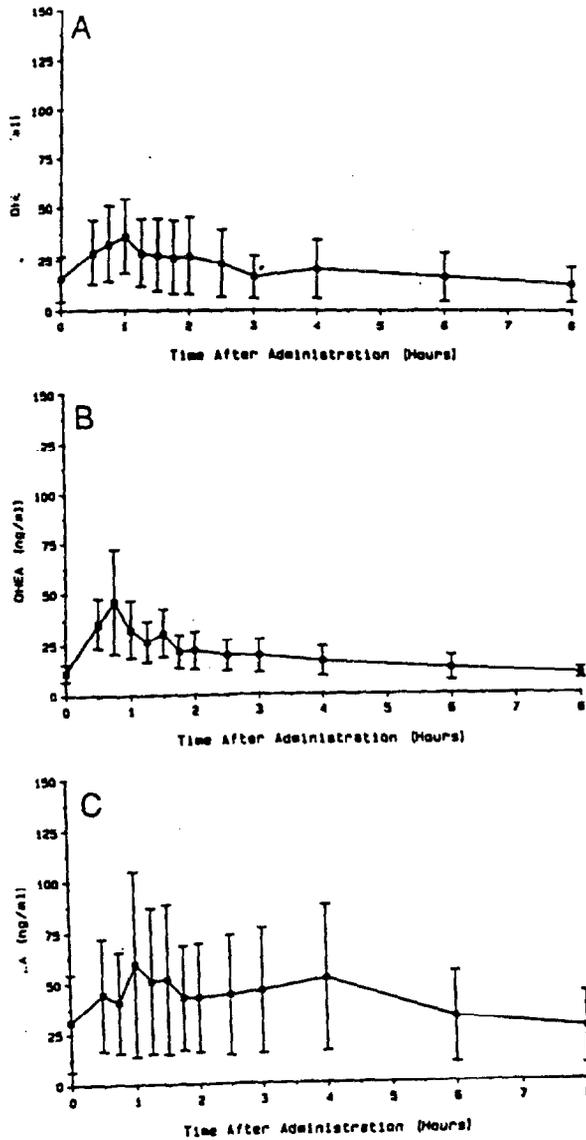


FIG. 1. Mean steady-state serum dehydroepiandrosterone (DHEA) concentrations ( $\pm$ SEM) during an 8-h period after dosing five subjects each at (A) 250, (B) 500, or (C) 750 mg DHEA every 8 h.

Concentrations were generally 5–10 times higher than the pretreatment baseline values (Figs. 1 and 2), and 24-h urinary 17-ketosteroid amounts were generally 30–100 times higher than baseline values (data not shown).

However, dose proportionality was not observed in the serum levels achieved in the three dosing groups. Pharmacokinetic parameters for the three dosage groups and ratio of the means for these values relative to the 750 mg/day dose level are summarized in Table 4. Ratios of urinary 17-ketosteroid

concentrations for the three dosage groups were 1, 1.4, and 2.67, respectively. Of note, there were four subjects (one in the 750-mg dose group, two in the 1,500-mg group, and one in the 2,250-mg group) whose steady-state DHEA concentration was 3–15 times higher than that of the other subjects in their respective groups. Two of these four individuals with high steady-state serum DHEA concentrations compared with 4 of 19 among those with categorically lower DHEA concentrations had sustained increases in absolute CD4 lymphocyte count above

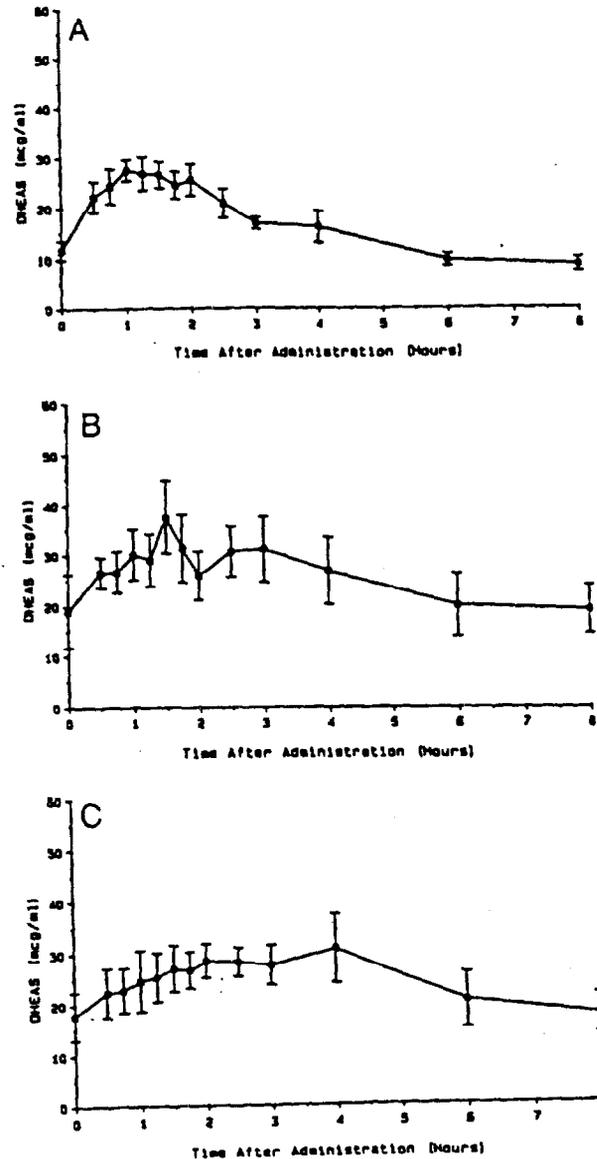


FIG. 2. Mean steady-state serum dehydroepiandrosterone sulfate derivative (DHEA-S) concentrations ( $\pm$ SEM) during an 8-h period after dosing five subjects each at (A) 250, (B) 500, or (C) 750 mg DHEA every 8 h.

TABLE 4. Dose proportionality of serum dehydroepiandrosterone (DHEA) levels as reflected by range of AUC(8),  $C_{ss}$ ,  $C_{min}$ , and  $C_{max}$  values and ratio of mean values relative to the lowest (750 mg/day) dose

	Daily dose (mg/day)	DHEA		DHEA-S	
		Range	Ratio	Range	Ratio
AUC(8)	750	35-590	1	81-130	1
	1,500	48-330	0.9	115-363	1.55
	2,250	86-1,190	1.98	101-314	1.51
$C_{min}$	750	3-47	1	7-13	1
	1,500	4-20	0.71	9-37	1.93
	2,250	3-95	1.94	4-32	1.74
$C_{max}$	750	9-105	1	22-35	1
	1,500	13-145	1.3	23-56	1.17
	2,250	18-198	1.41	21-52	1.1
$C_{ss}$	750	4-74	1	10-22	1
	1,500	6-41	0.9	14-45	1.55
	2,250	11-149	1.98	13-39	1.51

AUC(8), area under the curve for 0-8 h in ng-h/ml for DHEA and  $\mu\text{g-h/ml}$  for DHEA-S;  $C_{min}$ , serum trough concentration in ng/ml for DHEA and  $\mu\text{g/ml}$  for DHEA-S;  $C_{max}$ , serum peak concentration in ng/ml for DHEA and  $\mu\text{g/ml}$  for DHEA-S;  $C_{ss}$ , steady-state serum concentration in ng/ml for DHEA and  $\mu\text{g/ml}$  for DHEA-S.

their baseline value throughout the study period ( $p = 0.27$ ). No other correlative trend between steady-state DHEA concentration and immunologic or virologic outcome or toxicity was observed.

## DISCUSSION

In this open-label, uncontrolled phase I trial, DHEA was well tolerated and did not cause any serious drug-related adverse events. The doses of DHEA administered were chosen to bracket the maximum tolerated dose previously reported for non-HIV-infected patients (9-12). Side effects attributable to DHEA therapy were minimal. DHEA administration did not produce any sustained increases in absolute CD4+ lymphocyte counts nor reduction in p24 antigenemia or  $\beta_2$ -microglobulin levels (markers previously used to demonstrate in vivo antiretroviral effect for dideoxynucleoside agents), although we did note a transient decrease in serum neopterin levels and a transient dose-related improvement in lymphocyte response to CMV recall antigen.

Studies of the natural history of HIV infection have convincingly demonstrated that both absolute CD4+ lymphocyte count and serum neopterin concentration are powerful predictors of subsequent progression of HIV disease (13,14). Absolute CD4 count also has established utility as a marker of improved clinical outcome with dideoxynucleoside

therapy for HIV infection (15,16). Although studies have reported significant decreases in serum neopterin associated with dideoxynucleoside therapy, it is not known whether such decreases actually reflect clinical efficacy (15). DHEA does not appear to inhibit HIV reverse transcriptase (the mechanism by which dideoxynucleoside agents ameliorate HIV disease) (4). In fact, the mechanism by which DHEA might inhibit HIV activity might be more immunostimulatory than antiviral based (2-4). Nevertheless, our immunologic observations in this trial could have reflected an in vivo inhibitory effect of DHEA on HIV replication or on HIV-induced damage to the immune system.

On the other hand, given the multiple outcome variables analyzed for the relatively small patient sample and the lack of randomization in this phase I tolerance and pharmacokinetics trial, no conclusions regarding DHEA efficacy should be made. As an example, we observed a trend toward less absolute CD4 lymphocyte count decline in patients receiving higher DHEA doses. However, in a large, randomized, placebo-controlled trial of zidovudine for a patient population very similar to that enrolled in the phase I DHEA trial (early symptomatic HIV disease and 200-500 CD4+ lymphocytes/ $\mu\text{l}$ ), absolute CD4 counts in the control, placebo-assigned patients declined by a median 5 cells/month (17). In contrast, patients in the "control," lowest-dose group studied in the phase I DHEA trial (whose immune system would not be expected to decline faster than that of placebo-treated patients in the other trial) had a median CD4+ decline of 31 cells/month. This suggests that our lowest-dose group, in fact, cannot be considered a "control" group generalizable to the larger population of mildly symptomatic HIV-infected patients.

The pharmacokinetic results in this trial revealed that in patients with early symptomatic HIV disease, dose proportionality was not observed in serum time-concentration curves and that two subpopulations may have comprised the study cohort, one evidencing significantly higher bioavailability for a given dose of DHEA than the other. Confirmation of this observation would require evaluation of DHEA pharmacokinetics in a larger study population, with a protocol specifically designed for the purpose.

In conclusion, given the epidemiologic observation that risk of progression to AIDS is independently associated with subnormal endogenous levels of DHEA (7), the possibility that oral adminis-

tration of DHEA may have beneficial effects on HIV disease (3,4), and the apparent safety of DHEA as demonstrated in this phase I trial, further studies, perhaps in combination with antiretroviral agents, seem warranted.

**Acknowledgment:** We thank Joe Bender, Chris Bliven, Georgette Skellinger, Joseph Cecere, and Bridget Stringer for their help. This study was supported by a grant from Elan Pharmaceuticals.

#### REFERENCES

- Schwartz AG, Pashko L, Whitcomb JM. Inhibition of tumor development by dehydroepiandrosterone and related steroids. *Toxicol Pathol* 1986;14:357-62.
- Loria RM, Inge TH, Cook SS, Szakal AK, Regelson W. Protection against acute lethal viral infections with the native steroid dehydroepiandrosterone (DHEA). *J Med Virol* 1988;26:301-14.
- Daynes RA, Dudley DJ, Araneo BA. Regulation of murine lymphokine production in vivo: II. Dehydroepiandrosterone is a natural enhancer of IL-2 synthesis by helper T cells. *Eur J Immunol* 1990;20:793-802.
- Schinazi RF, Eriksson BFH, Aronold BH, Lekas P, McGrath MS. Effect of dehydroepiandrosterone in lymphocytes and macrophages infected with human immunodeficiency virus. In: Kalimi M, Regelson W, eds. *The biological role of dehydroepiandrosterone (DHEA)*. Berlin: Walter de Gruyter (in press).
- Merril CR, Harrington MG. Plasma dehydroepiandrosterone levels in HIV infection [Letter]. *JAMA* 1989;261:1149.
- Bricaire F, Rouveix B, Pignal R. Taux des hormones sexuelles et du cortisol chez les malades atteints de syndrome d'immunodéficience acquise. *Presse Med* 1988;17:1540.
- Jacobson MA, Fusaro RE, Galmarini M, Lang W. Decreased serum dehydroepiandrosterone is associated with an increased progression of human immunodeficiency virus infection in men with CD4 cells counts of 200-499. *J Infect Dis* 1991;164:864-8.
- Mulder JW, Frissen PHJ, Krijnen P, et al. Dehydroepiandrosterone as predictor for progression in AIDS in asymptomatic human immunodeficiency virus-infected men. *J Infect Dis* 1992;165:413-8.
- Cohen HN, Hay ID, Beastall GH, Thomson JA. Failure of adrenal androgen to induce puberty in familial cytomegalic adrenocortical hypoplasia. *Lancet* 1982;2:1471-2.
- Koo E, Feher KG, Feher T, et al. Effect of dehydroepiandrosterone on hereditary angioedema. *Klin Wochenschr* 1983;61:715-7.
- Mochizuki M, Honda T, Deguchi M, et al. A study on the effect of dehydroepiandrosterone sulfate on so-called cervical ripening. *Acta Obstet Gynecol Scand* 1978;57:397-401.
- Nestler JE, Barlasini CO, Clore JN, et al. Dehydroepiandrosterone reduces serum low density lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. *J Clin Endocrinol Metab* 1988;66:57-61.
- Fahey JL, Taylor JMG, Detels R, et al. The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1. *N Engl J Med* 1990;322:166-72.
- Moss AR, Bacchetti P, Osmond D, et al. Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort. *Br Med J* 1988;296:745-50.
- Jacobson MA, Bacchetti P, Kolokathis A, et al. Surrogate markers for survival in patients with AIDS and AIDS related complex treated with zidovudine. *Br Med J* 1990;302:73-8.
- Weiss R, Mazade L, eds. *Surrogate endpoints in evaluating the effectiveness of drugs against HIV infection and AIDS*. Washington, DC: Institute of Medicine, National Academy Press, 1990.
- Fischl MA, Richman DD, Hansen N, et al. The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic human immunodeficiency virus type 1 (HIV) infection: a double-blind, placebo-controlled trial. *Ann Intern Med* 1990;112:727-37.