

The Antiviral Drug Docosanol as a Treatment for Kaposi's Sarcoma Lesions in HIV Type 1-Infected Patients: A Pilot Clinical Study

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ABSTRACT

Docosanol inhibits a broad spectrum of lipid-enveloped viruses *in vitro* including HSV-1, HSV-2, VZV, CMV, HHV-6, and HIV-1. These observations led us to conduct a pilot clinical study with docosanol 10% cream as a topical treatment for Kaposi's sarcoma (KS) in HIV-1-infected patients. In this open-label study 28 cutaneous KS lesions in 10 HIV-1-infected patients were treated topically five times daily for 4 weeks with evaluation of lesion characteristics of area, edema, and color. All patients elected to enroll in an extended treatment protocol and continued to treat for up to 35 weeks. Within 28 days, 2 of 10 patients exhibited a partial response based on standardized criteria exhibiting 74 to 83% reductions in total target lesion areas. With extended treatment, a partial response was exhibited in two additional patients where total target lesion area was reduced by 52% in one patient and target lesions in another patient that had been large, swollen, and painful at study initiation were no longer visible. No patient experienced disease progression or signs of visceral disease. The average percent decrease in lesion area for all target lesions was 20% ($p < 0.01$). A patient's response to therapy appeared to be independent of anti-HIV regimen, HIV viral load, or previous KS treatments. These results suggest that docosanol merits further investigation as a potential topical therapy in the treatment of AIDS-associated Kaposi's sarcoma lesions.

INTRODUCTION

DOCOSANOL (*n*-docosanol, 1-docosanol, behenyl alcohol) is a 22-carbon fatty alcohol that inhibits a broad spectrum of lipid-enveloped viruses.¹ Formulated as docosanol 10% cream, it has recently been approved by the U.S. Food and Drug Administration as a topical treatment for recurrent oral-facial herpes simplex infections (trade name Abreva™). Its efficacy in reducing the healing time and symptoms of oral-facial herpes simplex infections has been demonstrated in Phase 3 placebo-controlled clinical trials² and, previously, in a Phase 2 clinical trial.³ The drug has an excellent safety profile in the clinic, and no toxic potential is indicated from the results of extensive and comprehensive toxicology studies.⁴

In vitro antiviral activity of docosanol has been demonstrated against a number of lipid enveloped viruses.^{1,5–8} Susceptible viruses include HIV-1, herpes simplex viruses (HSV) 1 and 2, cytomegalovirus, varicella zoster virus, respiratory syncytial

virus, and human herpesvirus (HHV) 6. Non-lipid-enveloped viruses including poliovirus, adenovirus, and reovirus are resistant to inhibition by the compound. Lipid-enveloped viruses that enter cells by endocytic means also resist inhibition by docosanol. Studies indicate that docosanol has a novel mechanism of action, exerting its anti-HSV activity predominantly by interfering with the process of viral fusion with the host cell.^{1,5,8,9}

Kaposi's sarcoma (KS) is the most common tumor in HIV-1-infected individuals and contributes substantially to the morbidity and mortality suffered in patients with AIDS.¹⁰ The cutaneous lesions characterizing the disease can be numerous, disfiguring, and painful. The etiology of the disease appears to have an infectious component involving both HIV-1 and HHV-8.^{11–15} HIV-1 infection may increase levels of several cytokines, including tumor necrosis factor interleukin-1, interleukin-6, and basic fibroblast growth factor that may promote the growth of KS cells.¹⁶ DNA sequencing studies,^{17,18} have revealed a close association between KS and HHV-8, also re-

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ferred to as Kaposi's sarcoma-associated herpesvirus (KSHV), and it is becoming accepted that HHV-8 is necessary but not sufficient for development of KS neoplasms.^{14,15}

The optimal treatment for KS depends on the severity of the disease and the immunological status of the patient.¹⁹ Patients with relatively discrete mucocutaneous KS can be effectively treated with local therapies including intralesional chemotherapy, surgical excision, and radiotherapy.^{19–21} Patients with advanced KS, including patients with widespread mucocutaneous disease or visceral disease, are generally treated with systemic chemotherapy with cytotoxic agents such as liposomal anthracyclines, vinca alkaloids, or paclitaxel.^{19,22–25} Other treatment options include interferons, human chorionic gonadotropin, all-*trans*-retinoic acid (tretinoin), 9-*cis*-retinoic acid, granulocyte-macrophage colony-stimulating factor, and whole body hyperthermia.^{19,26–28} Panretin gel has received FDA approval for topical treatment of KS lesions.²⁹ Considering the inhibitory effects of docosanol on viral replication of HHV-6 and HIV-1, docosanol might also be clinically effective in the treatment of AIDS-associated KS in patients with discrete lesions while lacking the toxicity or invasiveness of the above treatments. We, therefore, initiated the pilot clinical trial reported here to examine the safety and efficacy of topically applied docosanol 10% cream in the treatment of cutaneous KS in HIV-1-infected patients.

MATERIALS AND METHODS

Study medication

Each gram of docosanol 10% cream contains 100 mg docosanol formulated into a white, nonstaining, moisturizing cream that is easily applied and is readily absorbed into skin and mucous membranes.

Patients

HIV-1-positive male patients over 18 years of age with clinically determined cutaneous KS lesions confirmed by a positive biopsy were screened and enrolled at a single study site (Scolaro Medical Coalition, Beverly Hills, CA). Eligible patients were otherwise clinically stable with no evidence of active opportunistic infection as documented by medical history, physical examination, and clinical laboratory examination performed at baseline. Patients with known systemic KS disease were specifically excluded. Patients were also excluded if they had a history of chronic alcoholism or drug abuse. Patients stabilized on an antiretroviral regimen with no change in regimen within 14 days prior to study initiation were eligible to participate but were to abstain from new antiretroviral or KS treatments during the study period.

Study design and procedures

All eligible patients were dispensed docosanol 10% cream to be applied five times per day for 28 days. Patients were advised that they could treat all of their current as well as any new cutaneous KS lesions that might occur. They were instructed to apply enough cream to cover the entire lesion plus approximately one-half inch around the lesion border. The first

dose was applied under the direction of the investigator and/or the research nurse. Patients kept a diary to record the date and time of each application. The protocol specified that those patients who completed the 28-day trial and who the investigator judged would benefit from continued treatment were eligible to continue treatment under an extended use protocol.

The number, area, and appearance of all KS lesions were recorded at study enrollment. Lesions were numbered and two or three target lesions that were easily accessible and previously untreated with either local radiation or topical chemotherapy were selected by the investigator at study enrollment to be examined for clinical response to therapy. All patients were to be assessed once weekly. The target lesion dimensions and appearance [i.e., lesion-associated edema, color, and lesion nodularity (raised versus flat)] were to be recorded during these visits.

Efficacy endpoints

The primary efficacy assessment was the proportion of patients experiencing a partial or complete response using protocol-defined criteria. The protocol specified that clinical response of the target lesions to treatment was to be graded relative to baseline as complete response [CR] (complete resolution of target lesions with histological confirmation), partial response [PR] (loss of lesion color and/or $\geq 25\%$ reduction in lesion area of target lesions), no response [no change in color or area of target lesions (these patients are also referred to as stable)], or progression (increase in area or vascularization of target lesions). Because this differs from the standardized uniform evaluation and response assessment criteria (ACTG response criteria) for KS, the data are evaluated here according to standard accepted criteria. The major difference is that a partial response is defined by ACTG as a $\geq 50\%$ decrease in the number of lesions that lasted for at least 4 weeks, or complete flattening of $\geq 50\%$ of all previously raised lesions, or a $\geq 50\%$ decrease in the sum of the products of the largest perpendicular diameters of the marker lesions and no new lesions or new visceral sites of involvement and no new worsening of tumor-associated edema or effusion.

Lesion area was calculated from the product of two perpendicular diameters, which were measured using a single calibrated slide caliper. Total lesion area for each patient was calculated by summation of the individual target lesion areas. Change in mean lesion area from baseline was calculated for the individual target lesions and also for total lesion area by patient.

Lesion color was recorded generally as purple, burgundy, deep red, pink, brown, or tan. Lesions that began as purple, burgundy, or deep red and were later described as tan or brown were interpreted to have undergone a loss of lesion color.

Statistical analysis

Demographic information and patient medical history information were summarized for the study group. Lesion area and appearance were also summarized.

Efficacy analysis included all patients who had baseline and Week 4 (final) visit ($N = 10$). A paired, two-tailed *t*-test was used to assess the change in lesion area from baseline to trial endpoint. Safety evaluations were based on all treated patients ($N = 13$). Statistical efficacy analysis was not conducted on data obtained from the extended protocol.

Safety assessments

Safety assessments were to be made based on the reporting of adverse events and from clinical laboratory measurements including blood chemistry, urinalysis, and hematology at weekly clinic visits.

RESULTS

Characteristics of study patients

Thirteen HIV-1-infected men with a mean age of 39 years (range 27 to 52 years) were enrolled in the trial. Ten patients completed the 28-day treatment. Three discontinued prematurely because of conflicts with protocol requirements. The disease characteristics of those patients completing the study are summarized in Table 1. KS was confirmed by histopathological evaluation in all patients (e.g., see Fig. 1A). In 8 of the 10 patients, KS was the AIDS-defining illness and had been present for 1 year or more. Seven of the 10 patients had a history of prior opportunistic infections. All patients presented with multiple cutaneous KS lesions (2 to 21) with no oral or nodal lesions. One patient reported severe tumor-associated edema and pain and a second patient reported severe tumor-associated pain. One to two nodular lesions were described for each of three patients, however, only one of the nodular lesions was selected as a target lesion. Of the patients who completed the study, eight were concurrently receiving multidrug antiretroviral treatment therapy; in six of these patients the regimen included a protease inhibitor. The antiretroviral regimens in the eight such treated patients had been stable for at least 2 months in all but one patient. Two patients were not receiving concomitant antiviral therapy.

Patient response

The area, color, and characteristics of the 28 lesions evaluated during the treatment period at baseline and at the 4-week visit are summarized in Table 2. Assessments made at other weekly intervals throughout the study are not shown. According to standardized criteria, two patients exhibited a PR based on >50% reduction in total target lesion area (patients WEB and D-D whose total target lesion areas were reduced 74% and 83%, respectively). Loss of lesion color was observed in one patient, SHC. By the 28-day visit the total target lesion area in SHC had decreased by 16% and the severe edema and pain around the lesions at baseline were largely resolved.

None of the patients manifested progression of their target lesions, as indicated by changes in area or color, or developed any signs of visceral dissemination of KS during treatment in either the 28-day treatment period or during the extended treatment study (although one patient, LMK, developed a single new KS lesion at an untreated cutaneous site during the 28-day treatment period). No patients exhibited a complete response. The quantitative and qualitative treatment effects observed follow.

Lesion area and number. None of the patients exhibited a decrease in the total number of KS lesions. The average individual lesion area for the 28 target lesions was 329.9 mm² at baseline (range = 12 to 1216 mm²), and decreased by a mean

of 34.2 mm² (range = -280.0 to 0.0 mm²) during the 28-day docosanol 10% cream treatment period with an average percent decrease in lesion area of 20%. The decrease in mean lesion area was statistically significant ($p < 0.01$).

The mean of patients' total target lesion area (the sum of the product of two perpendicular diameters for all target lesions) was 923.7 mm² at baseline and decreased by 95.7 mm². The largest decrease in total lesion area was 355 mm² and the smallest was 0; the average percent decrease in total lesion area was 23% between baseline and the final visit. Borderline statistical significance ($p = 0.057$) was found in the analysis of change from baseline total lesion area by patient.

Lesion color. In all but one patient (JTG; three lesions) analysis of weekly color assessments of target lesions revealed a progressive lightening or fading in color with treatment. None of the target lesions became darker in color during the treatment period. Of the 28 target lesions evaluated, 16 (57%) faded from deep red, burgundy, or purple at baseline to pink, brown, or tan by 28 days. Five lesions faded to a tan or brown color.

Histological evaluation. Lesions biopsies provided histopathological confirmation of KS in all patients. Following treatment, biopsies of lesions in patients exhibiting partial responses were taken for histological evaluation. For example, sections of a KS lesion from patient WEB taken prior to treatment shows spindle cell proliferation that forms vascular slits with extravasated erythrocytes (Fig. 1A). The lesion extended into the superficial panniculus. Hemosiderin pigment was noted and chronic inflammatory cells were identified. The lesion appeared to be in the plaque stage of development. Following 4 weeks of treatment, skin sections (Fig. 1B) of a KS lesion from the same patient demonstrated improvement. The pathologist's report described focal residual KS characterized by a few irregular dilated blood vessels accompanied by a few vascular slits in the superficial papillary dermis with extravasated erythrocytes and hemosiderin pigment. The lesion appeared to be confined to the papillary dermis.

Edema. Lesion-associated edema was present at baseline in one patient (SHC). Target KS lesions were located on his right foot and these lesions were associated with localized lymphatic obstruction and lymphedema with massive edema up to mid-calf. The three target lesions ranged in area from 200 to 1200 mm², were purple in color, firm to the touch, and caused disabling pain at study initiation. This patient experienced a partial resolution of the lymphedema following 1 week of docosanol treatment. By 28 days, the edema was largely resolved, the lesions were no longer painful, and total target lesion area was reduced 16%. After 35 weeks of treatment the lesions were reported to be no longer visible (see below). A second patient reported decreased lesion-associated pain by the 28-day visit (WBL).

Other lesion characteristics. In this study, no baseline lesions were described as raised and only one lesion was reported as nodular at baseline so effects of treatment on decreasing the vertical dimension of the lesion could not be assessed. The target lesion described as nodular at baseline was reduced 44% in

TABLE 1. DISEASE CHARACTERISTICS OF STUDY PATIENTS

<i>Patient/ No.</i>	<i>HIV viral load (copies/ml)</i>	<i>CD4 count</i>	<i>Prior opportunistic infections</i>	<i>On-study antiviral medications</i>	<i>Prior KS treatments</i>	<i>Total lesion count</i>	<i>Tumor associated pain/or edema^a</i>	<i>Study response^b</i>
WEB (001)	25,657	34/ μ l	Pulmonary cryptococcosis, pulmonary MAC, herpes zoster ophthalmic	Stavudine, zalcitabine, saquinavir, hydroxyurea, ganciclovir, acyclovir	HCG, radiation	4	ND ^c	PR
D-D (006)	<400	138/ μ l	Hepatitis A and B, HSV, syphilis, gonorrhea, bacterial pneumonia, leukoplasia, tinea barbaris capitis, onychomycosis	Zalcitabine, acyclovir, saquinavir, indinavir, stavudine, ganciclovir	None	5	ND	PR
CKW (007)	NA ^c	455/ μ l	Herpes zoster, hepatitis A, amebic dysentery, rosacea	Indinavir, zidovudine	None	5	ND	Stable/PR extended
SHC (008)	<200	549/ μ l	Candidiasis	Indinavir, acyclovir, zidovudine, lamivudine	HCG	8	Pain, edema toes	Stable with decreased pain and edema/PR extended
DMS (002)	NA	199/ μ l	None	Zidovudine, lamivudine, acyclovir	Radiation	6	ND	Stable
TLM (009)	831	284/ μ l	Herpes zoster, CMV, folliculitis	Indinavir, acyclovir, zidovudine, lamivudine	Unknown chemo., HCG	21 (1 nodular)	ND	Stable
JTG (010)	NA	266/ μ l	Hepatitis	Zidovudine, lamivudine	None	3	ND	Stable
TEM (011)	NA	NA	Cyclosporidion diarrhea, HSV, gonorrhea, molluscum	Acyclovir, zidovudine, zalcitabine, indinavir	Radiation, vinblastine	15 (2 nodular)	ND	Stable
WBL (012)	NA	NA	None	None	None	18	Painful lesions	Stable with decreased pain
LMK (014)	453,751	47/ μ l	None	None	None	2 (1 nodular)	ND	Stable

^aTarget lesion characteristics are listed in Table 2.

^bBy ACTG criteria.

^cNA, Not available; ND, none described.