Topical Treatment of Cutaneous Lesions of Acquired Immunodeficiency Syndrome–Related Kaposi Sarcoma Using Alitretinoin Gel

Results of Phase 1 and 2 Trials

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Objective: To evaluate the efficacy and safety of topical alitretinoin gel (9-cis-retinoic acid [LGD1057], Panretin gel; Ligand Pharmaceuticals, Inc, San Diego, Calif) in cutaneous Kaposi sarcoma (KS).

Design: Open-label, within-patient, controlled, dose-escalating phase 1 and 2 clinical trials. In all patients, 1 or more cutaneous KS lesions were treated with alitretinoin gel, and at least 2 other lesions served as untreated controls for up to 16 weeks. Alitretinoin (0.05% or 0.1% gel) was applied twice daily for the first 2 weeks and up to 4 times daily thereafter, if tolerated.

Setting: Nine academic clinical centers.

Patients: One hundred fifteen patients with biopsy-proven acquired immunodeficiency syndrome (AIDS)–related KS.

Main Outcome Measures: AIDS Clinical Trials Group response criteria.

Results: Statistically significant clinical responses were observed in 31 (27%) of 115 patients for the group of treated index lesions compared with 13 (11%) for the group of untreated control lesions ($P<.001$). Responses occurred with low CD4+ lymphocyte counts (<200 cells/µL) and in some patients with refractory response to previous systemic anti-KS therapy. The incidence of disease progression was significantly lower for treated index lesions compared with untreated control lesions (39/115 [34%] vs 53/115 [46%]; $P=.02$). Alitretinoin gel generally was well tolerated, with 90% of treatment-related adverse events confined to the application site and only mild or moderate in severity.

Conclusions: Alitretinoin gel has significant antitumor activity as a topical treatment for AIDS-related KS lesions, substantially reduces the incidence of disease progression in treated lesions, and is generally well tolerated.

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The appearance of Kaposi sarcoma (KS) in homosexual men1 prompted the recognition of acquired immunodeficiency syndrome (AIDS). Kaposi sarcoma remains the most common AIDS-associated malignant neoplasm,2 and it has now been shown to be associated with infection with human herpesvirus 8.3 Because cutaneous KS lesions serve as a visible sign of HIV infection, their presence may cause significant psychological distress.4 Thus, treatment of KS lesions is desired by many HIV-infected patients, even when the extent of disease is not life threatening. Systemic KS treatments may cause further immunosuppression and adverse effects.5 Local therapies for KS, such as cryotherapy, radiation therapy, intralesional vinblastine sulfate, and laser ablation, require administration by physicians and may result in pain, scarring, ulceration, or unwanted pigmentation changes.6-9

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Despite the fact that topical chemotherapy for cancer can be a routine practice, as in mechlorethamine hydrochloride (nitrogen mustard) and Carmustine for cutaneous T-cell lymphoma, topical retinoid therapy for tumors is relatively new. The successful use of retinoic acid (vitamin A$_2$, acid) in the treatment of tongue lesions (hairy leukoplakia) in patients with AIDS or AIDS-related complex already has established a precedent for treating AIDS-related lesions by means of topical application of a retinoid.10 In a preliminary pi-
lot study of topical 1% tretinoin (all-trans-retinoic acid) gel in 8 patients with AIDS-related cutaneous KS, most patients experienced at least partial responses. These studies provided sufficient rationale for the evaluation of alitretinoin gel (9-cis-retinoic acid) in the treatment of cutaneous lesions of KS.

Retinoids may have profound effects on cellular differentiation and on programmed cell death through the regulation of gene transcription and interaction with transcription factors. Retinoids mediate their effects by binding to specific nuclear hormone receptors, which include α-, β-, and γ-retinoic acid receptors (RARs), and α-, β-, and γ-retinoid X receptors (RXRs). In contrast, all-trans-retinoic acid (tretinoin, the stereoisomer of 9-cis-retinoic acid) binds primarily to RARs, with a very low affinity for RXRs. Isotretinoin (13-cis-retinoic acid) indirectly activates RARs and has no active form of RXRs.

Certain retinoids, including all-trans-retinoic acid, have been shown to inhibit the growth of KS cell lines in vitro. Phase 2 studies have demonstrated conflicting results of clinical efficacy with orally administered tretinoin in AIDS-related KS. Clinical trials also have demonstrated that orally administered isotretinoin has low activity, considerable toxicity, and limited cosmetic benefit in poor-risk patients with AIDS-associated KS.

To investigate the potential clinical usefulness of topically applied 9-cis-retinoic acid for AIDS-associated KS, phase 1 and 2 dose escalation studies were conducted with alitretinoin gel at 9 study centers in the United States. The combined results of these studies, using nearly identical protocols, are reported herein.

RESULTS

PATIENT DEMOGRAPHICS

A total of 115 men with AIDS-related KS were enrolled at 9 centers. Demographic variables are described in the following tabulation:

EXCLUSION CRITERIA

Exclusion criteria included radiation therapy or intraleSIONAL chemotherapy for the lesions in the preceding 4 weeks; systemic or topical treatment of the lesions with vitamin A or other retinoid class drugs within the preceding 3 weeks; systemic treatment with an investigational drug study within the preceding 30 days; and concurrent active serious infections. Other criteria excluded breastfeeding women and patients with serious intercurrent medical illnesses, such as significant symptomatic visceral KS (eg, pulmonary KS requiring systemic therapy), which would have interfered with the ability of the patient to perform the treatment program.

ADDITIONAL REQUIREMENTS

All patients were to use an acceptable method of contraception throughout the treatment period and for 3 months after therapy was discontinued. The use of potentially confounding therapies was prohibited during the treatment period, including other KS therapies, radiation therapy, concurrent anticancer drug therapy, retinoid class drugs, beta carotene compounds, and vitamin A doses of more than 15,000 IU/d.

TREATMENT REGIMEN

In these open-label, intrapatient controlled trials, patients were randomized to receive 0.05% or 0.1% alitretinoin gel twice daily for the first 2 weeks. Treatment beyond the initial 2-week period was escalated in increments of 2 treatment levels (Table 1) every 2 weeks to 0.1% olitretinoin gel 4 times daily or until the patient was using the most intensive regimen that was acceptable to and tolerated by them and that was judged to be safe by the investigator. In the event of a dose-limiting toxic effect, the frequency of application was reduced and/or the concentration of alitretinoin gel was lowered to 0.05% or 0.01%, as appropriate. The frequency of application and the gel concentration subsequently could be increased again, as tolerated.

INCLUSION CRITERIA

Patients who were HIV-positive by results of enzyme-linked immunosorbent assay and who had biopsy-proven KS were eligible for inclusion in the trial. Patients were at least 18 years of age, had a Karnofsky performance status of at least 60, and had at least 1 cutaneous KS lesion that served as a treated index lesion and at least 2 other cutaneous KS lesions with similar characteristics that served as untreated control lesions. These lesions were representative of the patient’s overall cutaneous KS disease.

Patients had acceptable hepatic function (bilirubin levels of no more than twice the upper limit of normal and aspartate aminotransferase and alanine aminotransferase levels ≤5 times the upper limit of normal), renal function (serum urea nitrogen level ≤2.5 times the upper limit of normal and serum creatinine level ≤3 times the upper limit of normal), and hematologic findings (hemoglobin level, ≥80 g/L without being transfusion dependent; neutrophil count, ≥0.90 × 10^9/L; and platelet count, ≥50 × 10^9/L). In addition, women of childbearing age had negative results of a serum pregnancy test within 7 days of initiating treatment and had used adequate contraception for at least the preceding 4 weeks.

All patients gave written informed consent to participate in the studies. The studies were conducted in compliance with good clinical practices and in accordance with the ethical principles of the governing institutional review boards and the Helsinki Declaration.

TABLE 1

PATIENT DEMOGRAPHICS
The intended duration of study treatment was 4 weeks, with an option to continue with additional 4-week treatment periods if the investigator judged the treatment to be of clinical benefit to the patient and without unacceptable toxicity. Control and treated lesions on each patient were matched for lesion characteristics and were representative of the patient’s overall cutaneous disease. The control lesions and up to 8 index-treated lesions were photographed on day 1 and after each 4-week period of study. After at least 8 weeks, control lesions could be switched from no treatment to treatment with alitretinoin gel if desired by the investigator.

Patients who consented to skin biopsy had postbaseline specimens taken from lesions that had shown clinical evidence of regression compared with baseline.

OUTCOME MEASURES

The primary unit of analysis was the patient, and the efficacy measure was the number of patients with responses for the measured index lesions, assessed according to the AIDS Clinical Trials Group (ACTG) criteria as applied to topical treatment of KS lesions.

PATIENT RESPONSES

Each patient’s cutaneous KS tumor response rate was determined by evaluating the groups of KS index and control lesion assessments in the context of ACTG response criteria for KS index lesions. Index and control lesions were evaluated on the basis of lesion area (product of the 2 largest perpendicular diameters) and height (macular, plaquelike, or nodular) for at least 2 untreated control lesions and at least 1 treated index lesion. Lesion responses were evaluated compared with baseline lesion status and required confirmation by 2 clinical observations at least 4 weeks apart. A clinical complete response required that no clinically detectable residual disease be present. A partial response required the fulfillment of one of the following criteria: 50% reduction in aggregate area of index lesions; 50% reduction in the number of raised lesions at baseline (ie, becoming completely flat); or, for patients with predominantly nodular lesions, 75% reduction in the number of nodular lesions at baseline (ie, becoming completely flat or plaquelike). Progressive disease was defined by a 25% increase, relative to the baseline value, in the aggregate area of index lesions or a 25% increase in the number of raised lesions. Stable disease was defined as any response not meeting the response assessment criteria for complete or partial response or progressive disease.

Secondary efficacy measures included time to onset of first response, duration of response, incidence of disease progression, and time to onset of disease progression.

Treatment-emergent adverse events were mapped to dictionary terms and body systems using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART-5) dictionary.26 Because COSTART-5 mapping classifies adverse events without regard to the site of topical drug application, some of the dictionary-specified conventions tend to exaggerate the nature and severity of the observed adverse events. Examples of the COSTART-5 mapping include swelling, edema, and inflammation that are assigned to edema in the cardiovascular body system (even when occurring only at the site of topical drug application); excoriations, crusting, eschars, fissures, and oozing are assigned to skin disorder; erythema, scaling, irritation, rash, and dermatitis are assigned to rash; bleeding is assigned to hemorrhage; and burning and pain are assigned to pain.

Dermal toxicity was graded as follows: grade 1 indicates scattered macular or papular eruption, or asymptomatic redness; grade 2, increased redness or edema; grade 3, very red or edema with or without vesiculation; and grade 4, deep red or swelling and edema with or without signs of bullae formation and necrosis.

STATISTICAL ANALYSIS

All patients who were enrolled, randomized, and dispensed study drug were included in the intent-to-treat analysis. The McNemar matched-pairs analysis was used to reflect the natural pairing of treated index and untreated control lesions on each patient.

Variable | Median (Range)
--- | ---
Age, y | 38 (25-64)
Time since KS diagnosis, mo | 11.2 (0-125)
No. of cutaneous KS lesions per patient | 8 (3-67)
No. of control index lesions | 2 (2-4)
No. of treated index lesions | 4 (1-64)
CD4+ lymphocyte count at baseline, cells/µL | 48 (0-1127)

These patients had 758 treated index lesions and 264 control lesions that were evaluated. The ethnic origin of the patients was 80% white, 16% Hispanic, 3% black, and 1% Native American. Baseline characteristics generally were well matched between the group of patients initially treated with 0.03% alitretinoin gel (n = 58) and the group initially treated with 0.1% alitretinoin gel (n = 57).

At baseline, 108 patients (94%) had at least 1 poor risk characteristic according to the ACTG staging classification system for tumor, immune status, and systemic illness.23 In this regard, 82% of patients had a history of at least 1 opportunistic infection or AIDS-related illness; 55%, at least 2 such events; and 36%, at least 3 such events. Seventy-five percent of patients had a baseline viral load of less than 1000 copies/mL.

Efficacy

Duration of Therapy

Continuation with therapy after the initial 4-week period was optional and dependent on investigator judg-
Table 1. Escalation of Treatment Levels*

<table>
<thead>
<tr>
<th>Treatment Level</th>
<th>Alitretinoin Gel Concentration, % wt/wt†</th>
<th>No. of Daily Applications</th>
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<tr>
<td>2</td>
<td>0.01</td>
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<td>3</td>
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<tr>
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<tr>
<td>6</td>
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</tr>
<tr>
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<td>0.05</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
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<tr>
<td>10</td>
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</tr>
<tr>
<td>11</td>
<td>0.1</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>0.1</td>
<td>4</td>
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</table>

*At the rate of 2 treatment levels every 2 weeks as tolerated.
†The 0.01% concentration was reserved as a recovery regimen in the event of treatment-limiting toxic effects.
‡The randomized initial dose levels were 0.05% twice daily and 0.1% twice daily.

Antiretroviral therapies increased, there was a trend to response to study treatment. As the number of concurrent antiretroviral agents patients received was assessed in the receiving agents that suppressed HIV, the number of antiretroviral therapy.

and number of raised lesions), concurrent antiviral therapy, and baseline index lesion characteristics (aggregate area and diameter, continued to have residual hyperpigmentation, especially in patients with more darkly pigmented skin.

Patient Response Rates

Thirty-one patients (27%) had responses for the group of treated index lesions vs only 13 (11%) for the group of untreated control lesions (P<.001), using ACTG criteria applied to the KS index lesions. Clinical complete responses were achieved in 3 patients (3%) for treated index lesions, but were not seen in untreated control lesions. Examples of patient responses are seen in Figure 1 through Figure 4. Two of the responding patients were refractory to previous systemic anti-KS therapy.

For response by lesion, 50 patients (43%) had at least 1 treated index lesion improve by at least 50% vs 19 patients (17%) having at least 1 control lesion respond. Thirteen patients (11%) had at least 1 treated index lesion completely resolve vs no complete resolutions among the control lesions.

The response rate with alitretinoin gel remained substantially higher than that observed with no treatment, even after consideration of the patients’ age, race, baseline Karnofsky performance status, baseline CD4+ lymphocyte counts, history of opportunistic infections or AIDS-related illnesses, baseline index lesion characteristics (aggregate area and number of raised lesions), concurrent antiviral therapy, and concurrent antiretroviral therapy.

Because patients entering this trial sometimes were receiving agents that suppressed HIV, the number of antiretroviral agents patients received was assessed in the response to study treatment. As the number of concurrent antiretroviral therapies increased, there was a trend toward a higher response rate for the untreated control lesions (P = .06) but not for the treated index lesions (P = .52). However, after grouping patients by the number of antiretroviral therapies (≤1 vs ≥2 agents), the patients’ response rate was significantly higher for the alitretinoin gel-treated lesions than for the untreated lesions (P = .007).

Responses to alitretinoin gel were achieved even in patients with low CD4+ lymphocyte counts. Indeed, 12 (39%) of 31 responding patients had a baseline CD4+ lymphocyte count of 50 cells/µL.

Although the study was not designed to compare response rates for different alitretinoin gel dose schedules, there was no apparent relationship between patients’ response rates and the last gel concentration or frequency of application used. However, all 3 patients who experienced a clinical complete response had been applying the 0.1% gel at least twice daily.

Among the 28 patients whose control lesions were treated with alitretinoin gel after at least 8 weeks of no treatment, the response rate increased from 3 (11%) with no treatment to 11 (39%) with alitretinoin treatment (P = .02). Control lesion measurements were reset to a new baseline at the time the treatment with alitretinoin gel began.

Nature of Response

Figures 1 through 3 show examples of typical KS lesions before and after periods of treatment with alitretinoin gel. Generally, the initial response to alitretinoin gel was a flattening of the KS lesion, without a reduction in its diameter. The borders of some lesions initially became obscured by retinoid-induced perilesional erythema. Typically, lightening of the lesion pigmentation occurred next, making it less apparent. Finally, lesion diameter decreased. Some lesions, although reduced in size and diameter, continued to have residual hyperpigmentation, especially in patients with more darkly pigmented skin.

Responses in multiple cutaneous lesions often were observed in the same patient during alitretinoin treatment. In a patient with numerous KS lesions of the trunk (Figure 1A), 2 distinct lesions on the left breast are shown as an example of a multiple response. A significant decrease in size and pigmentation of lesion 3T was seen after 4 weeks of alitretinoin gel therapy (Figure 1B), and the lesion had almost completely resolved by week 16 (Figure 1C). For KS lesion 4T (Figure 1D), simultaneous reductions in lesion size and pigmentation were observed after alitretinoin treatment (Figure 1E).

As shown in Figure 2, facial lesions responded to therapy with alitretinoin gel. In addition, alitretinoin was successful in treating chronic KS lesions on the lower extremities that had been painful (Figure 3).

An analysis of lesion sizes disclosed a difference in the size of control and treated index lesions in these clinical studies. The median lesion area for treated lesions was 576 mm², but was 151 mm² for control lesions. Because larger KS lesions generally are considered to be more refractory to KS treatment, the relatively larger size of the treated index lesions may lead to an underestimation of the alitretinoin response rate compared with the control response rate.
Response Rates for Patients Using Protease Inhibitors

The overall response rate by patient (≥50% of all lesions responding) was 13 (38%) for the group of alitretinoin-treated index lesions and 5 (15%) for the group of untreated control lesions for the 34 patients who reported taking at least 1 protease inhibitor concurrently. Figure 4 shows the response rates for individual treated index lesions and untreated control lesions in relation to the use of individual protease inhibitors. Although the cohort sample sizes are small, the alitretinoin gel treatment effect reached statistical significance for patients using any protease inhibitor ($P = .01$), for 2 of the 4 cohorts (saquinavir, $P = .008$; ritonavir, $P = .046$), and reached a statistical trend for indinavir ($P = .10$). Nelfinavir was taken by only 1 patient.

Onset and Duration of Response

Among the 31 patients who met the ACTG response criteria for treated index lesions, the median time to onset of first response was 33 days (range, 12-294 days), and the median time to best response was 43 days (range, 12-324 days). The median duration of patients' time using the study drug for treated index lesions was 98 days (range, 5-674 days). The relapse rate for patients responding for treated index lesions was 14 (45%) of 31. The 14 patients with relapsed disease had a median duration of disease control of 98 days (range, 64-336 days).
When considering all 31 patients responding for treated index lesions, the median duration of disease control was 168 days (range, 61-582 days). This duration was achieved even using the very conservative approach of the date of their last lesion assessment as equivalent to a date of relapse for the 17 patients without relapse.

**Disease Progression**

The incidence of disease progression was significantly lower for treated index lesions compared with untreated control lesions: 39 (34%) of 115 patients vs 53 (46%) \( (P = .02) \). The median time to onset of disease progression was also substantially longer in treated index lesions compared with untreated control lesions: 61 days (range, 12-236 days) vs 32 days (range, 14-327).

**TOLERABILITY AND SAFETY**

**Maximum Tolerated Dose**

Alitretinoin gel generally was well tolerated, with most patients achieving and maintaining at least twice-daily treatment with the 0.1% gel (Figure 5). Compliance with the maximum prescribed dose was high: 86% of patients complied with their highest prescribed dosing regimen. Forty-six (90%) of 51 patients were compliant when the maximum dose prescribed was 0.1% gel 4 times daily (qid), 1 (100%) of 1 with 0.1% gel 3 times daily, 28 (85%) of 33 with 0.1% gel 2 times daily (bid), 7 (54%) of 13 with 0.05% gel qid, and 17 (100%) of 17 with 0.05% gel bid.

**Adverse Events**

Most treatment-related adverse events (90%) were confined to the application site, and nearly all adverse events were of only mild or moderate severity. The most common adverse events were related to signs and symptoms...
of local irritation, including rash, pain, and skin disorders (Table 2). There were no treatment-related deaths or serious adverse events. This was not a randomized dose-response study, and no relationship between the incidence of treatment-related adverse events and the concentration of alitretinoin gel or the frequency of its application could be determined.

Fifty-four (47%) of 115 patients applied alitretinoin gel to a treated index lesion or a converted lesion that was on an area of skin often exposed to the sun, such as the face, hands, neck, or forearm. No treatment-related adverse events mapping to the COSTART-5 term of photosensitivity were reported.

Twenty-five treatment-emergent opportunistic infections or AIDS-related illnesses were reported by 21 patients, but none was judged to be related to the application of alitretinoin gel.

Treatment-Limiting Toxicity

There were no reported cases of systemic treatment-limiting toxicity, and 28 dermal treatment-limiting toxicity were reported in 23 patients. Of these, 9 patients had grade 2 dermal toxicity (increased redness and edema), 13 patients had grade 3 dermal toxicity (very red and edema with or without vesiculation), and 1 patient had grade 4 dermal toxicity (deep red, swelling, and edema with or without signs of bullae formation and necrosis) that were later judged by the investigator not to be related to the application of alitretinoin gel.

Discontinuation of Therapy

The initial 4-week treatment period was completed by 100 (87%) of 115 patients. Six of the patients assigned to receive 0.05% alitretinoin gel and 9 of those assigned to receive 0.1% alitretinoin gel withdrew from the study before completing treatment. According to the investigators, the most common reasons for patients discontinuing therapy at any time during the study were progression of KS (33% of 115 patients), withdrawal of consent (19%), noncompliance (9%), unavailability for follow-up (9%), adverse events (9%), stable disease (8%), and administrative reasons (5%).

Plasma Concentration of 9-cis-Retinoic Acid

The range and frequency of detection of quantifiable plasma levels of 9-cis-retinoic acid after treatment with alitretinoin gel (assay limit of detection, 0.25 ng/mL; highest level detected, 0.64 ng/mL) were comparable to the range and frequency of detection of plasma levels of 9-cis-retinoic acid in untreated individuals.27 There was no apparent relationship between the plasma levels of 9-cis-retinoic acid and the concentration of alitretinoin gel, the time elapsed since its application, the number of lesions treated, or the frequency or duration of its application. These data suggest that there was no measurable systemic absorption of topically applied alitretinoin gel, and that the low quantifiable levels of 9-cis-retinoic acid were likely due, at least in part, to dietary intake of retinoids affecting endogenous levels of 9-cis-retinoic acid. There was no apparent difference in response rates between patients with and without quantifiable levels of 9-cis-retinoic acid. Similarly, response rates for the group of control lesions were comparable between patients with and without quantifiable levels of 9-cis-retinoic acid, suggesting that the responses of control lesions were not due to systemic activity of topically applied alitretinoin gel.

The results of these studies indicate that alitretinoin gel has significant antitumor efficacy in the topical treatment of AIDS-related KS lesions. Patient responses continued to accrue with longer treatment duration, including the observation of new partial responses as late as 42 weeks while receiving alitretinoin therapy. Treatment with alitretinoin gel elicited durable responses and delayed the onset of disease progression in treated lesions. The efficacy of alitretinoin gel was not dependent on patient age, race, baseline Karnofsky performance status, baseline CD4+ lymphocyte counts, history of opportunistic infections or AIDS-related illnesses, baseline index lesion char-

![Figure 5. Maximum dose achieved. Most patients (78/115) achieved and maintained a maximum dose of at least twice-daily (bid) treatment with 0.1% alitretinoin gel. Asterisk indicates 9 of 115 patients entered into the intent-to-treat trial had unknown application schedules recorded by investigators; dagger, 3 times daily (tid) treatment was less likely to be the maximum tolerated dose than bid or 4 times daily (qid) treatment because, according to the protocol, tid treatment was prescribed only if a reduction in frequency of application was necessary due to concerns about toxic effects.](image-url)
characteristics, or concurrent antiviral therapies. Treatment with alitretinoin gel appears suitable for many patients with KS, including those with low CD4+ lymphocyte counts and those requiring therapy for facial or cosmetically exposed lesions. Responses also were reported in some patients who were refractory to previous systemic anti-KS therapy. In addition, because larger KS lesions generally are considered more refractory to KS treatment, the larger size of treated index lesions compared with untreated control lesions (data not shown) may have led to an underestimation of the alitretinoin gel response rate compared with controls.

Although this phase 1 and 2 study was not designed to examine the effects of concurrent antiretroviral therapy, the data exclude any confounding effect from antiretroviral use because of the analysis rules for response. For the purpose of statistical analysis of the primary efficacy end point for these studies, patients were considered responders only if they responded for the treated index lesions, and not for the group of untreated control lesions, ie, an intrapatient control design. Thus, if the patient met response criteria for both the group of treated index lesions and the group of untreated control lesions, that patient was excluded from the comparison of response rates for both groups of lesions. Although the sample sizes for patients taking concurrent protease inhibitors or antiretroviral agents were relatively small, the data presented support the efficacy of alitretinoin gel treatment in those patients with KS.

The clinical results and toxicity profile seen with the application of alitretinoin gel offer an attractive alternative to other locally destructive therapies, but with a lower risk for pain, ulceration, and residual scarring. Most local therapies for KS, such as cryotherapy or intralesional injections, are painful and require multiple office visits, unlike alitretinoin gel. For patients with large numbers of cutaneous lesions, systemic therapy is an option, although the adverse effects may be severe. Thus, although other treatments for AIDS-related KS offer palliative benefits, 0.1% alitretinoin gel is distinguished by its at-home, patient-administered application and the fact that clinical responses are achieved without residual scarring.

There was a bias against the efficacy of alitretinoin gel in the intrapatient control design, but the results still showed a statistically significant difference favoring alitretinoin gel–treated lesions. If a patient left the study before completing the evaluation period (16 weeks) because of progression of untreated control lesions, there was a bias against alitretinoin gel effectiveness, since the gel-treated lesions may have responded with continued therapy to the end of the evaluation period. However, if the patient withdrew from the study early due to adverse effects of alitretinoin gel, there was also a bias against alitretinoin gel efficacy, because treated lesions may have responded by the end of the evaluation period. Despite the bias against alitretinoin gel therapy resulting from the within-patient control design, a statistical response in favor of alitretinoin gel vs no treatment was found in patients with KS.

Although the therapeutic mechanism of alitretinoin gel on KS lesions is not established, biopsy specimens of KS lesions sampled after a clinical remission showed a reduction in angiogenesis, especially in the upper dermis. Retinoids are known to inhibit the growth of KS cell lines in vitro, and this effect may contribute to the clinical therapeutic effect. The mechanism through which retinoic acids inhibit the proliferation of KS cells may involve down-regulation of the expression of interleukin 6, an autocrine growth factor for KS cells. In addition, retinoids may influence the expression of virally encoded oncogenes that are important for the expression of KS.

In these studies, alitretinoin gel generally was well tolerated, with adverse events primarily of only mild or moderate severity and localized to the site of application. Only 9% of patients were discontinued from the study prematurely due to adverse events. Patients reported verbally that the self-administration and convenience of alitretinoin treatment were considered important aspects. Most patients achieved and maintained a maximum tolerated dose of at least twice-daily treatment with the 0.1% gel, and the overall rate of compliance with the maximum prescribed dose was high (86%). No treatment-related opportunistic infections, AIDS-related illnesses, or photosensitivity reactions were reported. The tolerability of alitretinoin gel may be attributable to the more focused physiological action of alitretinoin through specific retinoid receptors compared with other available retinoids.

Topical treatment with alitretinoin gel does not increase plasma levels of 9-cis-retinoic acid above endogenous levels, indicating a lack of significant systemic exposure and minimal potential for drug interactions. Local retinoid irritation of the surrounding skin did occur, as expected, but generally was mild in nature and reversible. The topical delivery and lack of measurable systemic exposure in excess of endogenous retinoid levels also mean that treatment with alitretinoin gel is not likely to exacerbate the complexity of antiretroviral therapy regimens.

Response rates of untreated control lesions were higher than expected and may be partially attributable to application of the study drug to these lesions (in violation of the protocol) by several patients. Also, some patients entering this trial were receiving anti–human immunodeficiency virus agents (eg, antiretroviral therapy) that can improve patient immune competence and KS in some reports. Among the untreated control lesions, there was a trend toward a higher response rate in patients receiving higher numbers of antiretroviral agents. After grouping patients with concomitant antiretroviral therapies into blocks of no more than 1 and at least 2 therapies, the patients’ response rate was significantly higher for the alitretinoin gel–treated lesions than for the control lesions. Regardless of whether the patient is receiving or can tolerate antiretroviral therapy, alitretinoin gel is beneficial to promote lesion clearing and for treatment of resistant or conspicuous lesions of concern to patients.

Alitretinoin is the only retinoid receptor panagonist to be tested clinically to date. The combined analysis of phase 1 and 2 studies reported herein has provided rationale for further clinical trials of this retinoid. The efficacy of 9-cis-retinoic acid for treatment of cutaneous lesions of AIDS-related KS subsequently has been demonstrated in 2 phase 3 clinical trials (S. Walmsley, FRCP, unpublished observations, December 1997). Re-
results from 2 phase 2 trials of orally administered 9-cis retinoic acid show that this form of the compound also has activity in AIDS-related KS. Alitretinoin gel is not a systemic therapy. It cannot treat visceral KS or prevent the development of new KS lesions where it has not been applied. Visceral KS disease was not monitored in this trial, and the appearance of new KS lesions was not considered part of the response assessment.

As the first topically applied and patient-controlled therapy approved by the Food and Drug Administration for cutaneous AIDS-related KS lesions, alitretinoin gel facilitates the treatment of such lesions on an outpatient basis. It also provides an opportunity for earlier intervention, particularly in patients whose lesions are not so extensive or debilitating as to warrant treatment with potentially toxic systemic therapy. Alitretinoin gel may be a first-line topical treatment for cutaneous lesions of AIDS-related KS. In more advanced disease, the potential role of alitretinoin gel as an adjunct to systemic therapy for the treatment of particularly troublesome or conspicuous cutaneous diseases is currently under investigation.

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