

## CASE REPORT

# Kaposi's Sarcoma Treated with Topical Alitretinoin

A González de Arriba, S Pérez-Gala, R Goiriz-Valdés, L Ríos-Buceta, and A García-Díez

*Servicio de Dermatología, Hospital Universitario de La Princesa, Madrid, Spain*

**Abstract.** Kaposi's sarcoma is a multifocal neoplastic process with four clinical variants, all of them induced by human herpes virus 8. Currently there is no treatment of choice and it depends on the extension and location of the lesions as well as on the clinical type of the disease. Alitretinoin gel 0.1% is approved for the treatment of cutaneous lesions of AIDS-associated Kaposi's sarcoma. The majority of its side effects appear at the site of application and can lead to therapy withdrawal. We report a case of Kaposi's sarcoma treated with topical alitretinoin that had a favourable evolution in spite of an intense local reaction.

**Key words:** Kaposi's sarcoma, alitretinoin.

## SARCOMA DE KAPOSI CLÁSICO TRATADO CON ALITRETINOÍNA TÓPICA

**Resumen.** El sarcoma de Kaposi es un proceso neoplásico multifocal del cual existen 4 variantes clínicas, todas ellas inducidas por el virus herpes humano tipo 8. En la actualidad no existe un tratamiento de elección y éste depende de la extensión y la localización de las lesiones, así como del tipo clínico de la enfermedad. La alitretinoína al 0,1% en gel está aprobada para el tratamiento de las lesiones cutáneas del sarcoma de Kaposi asociado a sida. La mayoría de sus efectos secundarios aparecen en el lugar de aplicación y pueden obligar a suspender el tratamiento. Presentamos un caso de sarcoma de Kaposi tratado con alitretinoína tópica con buena evolución pese a la intensa reacción local.

**Palabras clave:** sarcoma de Kaposi, alitretinoína.

## Introduction

Kaposi sarcoma (KS) has several clinical variants, all of them induced by human herpes virus type 8 (HHV8). The development of the disease is dependent on the patient's immunological status, among other factors not yet clearly determined. At present, there is no treatment of choice, and actual therapy will depend on the extent and location of the lesions, as well as the clinical type of the disease. Various therapeutic regimens have been used, among them, chemotherapy (CT), radiation therapy (RT), and interferon (IFN). In 1999 the U.S. Food and Drug Administration (FDA) approved 0.1% alitretinoin (9-*cis*-retinoic acid) gel for topical use in the treatment of AIDS-related KS lesions in the skin. This endogenous hormone binds to all known intracellular retinoid receptors, regulating the process of

cell differentiation and apoptosis.<sup>1-5</sup> We present a patient with KS who was treated with topical alitretinoin and progressed favorably.

## Case Description

We describe an 83-year-old woman diagnosed with Sjögren syndrome under treatment with methotrexate and prednisone. One month after initiating therapy, she consulted for the onset of various erythematous, purpuric plaques on the limbs, buttocks, and trunk. The patient was diagnosed with KS, with this confirmed by histopathological study. Additional tests included negative serology for human immunodeficiency virus (HIV), positive serology for HHV8 (IgG titer >640), CD4 lymphocyte counts of 1088/mm<sup>3</sup> (neutrophils, 500-900/mm<sup>3</sup>), and CD8 lymphocyte counts of 174 (neutrophils, 200-400/mm<sup>3</sup>). The polymerase chain reaction assay of the skin biopsy was positive for HHV8. The cutaneous lesions continued to increase in number and size, even though methotrexate had been discontinued, coinciding with the increase in the steroid dose. Therapy was initiated with IFN- $\alpha$ -2b (5-15 subcutaneous mIU 3 times a week) for 5 and a half months, but discontinued due to severe asthenia and grade II hematological toxicity according to the World

Correspondence:  
Ana González de Arriba  
Servicio de Dermatología  
Hospital Universitario de La Princesa  
Diego de León, 62  
28007 Madrid, Spain  
E-mail: anagdearriba@aedv.es

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Health Organization (WHO) scale. Radiotherapy with an electron beam was subsequently started, but the patient was unable to tolerate it. A decision was made to start therapy under compassionate use with 0.1% topical alitretinoin gel, which the patient applied to the distal lesions at the knees, since these were the most visible. This treatment caused a severe local reaction (Figure 1) with erythema, edema, and blistering (grade III) with only two applications daily. This reaction forced the patient to decrease the dose to only one application every 48 to 72 hours. Clinical progress was slow, but favorable, leaving residual hyperpigmentation after 5 months of treatment (Figure 2).

## Discussion

The therapeutic approach to KS treatment mainly depends on the individual needs of each patient. The factors involved in the choice of treatment are usually the following:

1. Tumor spread and growth rate, in particular, visceral involvement
2. Associated symptoms
3. Immune status
4. History of opportunistic diseases. Several approaches are taken: local (reserved for small and/or thin tumors) and systemic (for large/symptomatic tumors or those with visceral involvement). The various treatments for KS are summarized in Table 1.

Retinoids are structural or functional analogs of vitamin A that regulate genetic transcription through their intracellular receptors which behave as ligand-dependent transcription factors. These receptors belong to the steroid–thyroid family and a distinction is currently made between two groups: RAR (retinoic acid receptors) and RXR (retinoid X receptors). In turn, each group is divided into three subgroups ( $\alpha$ ,  $\beta$ , and  $\gamma$ ). RAR- $\gamma$  and RXR- $\alpha$  are found in the human skin.

Three generations of retinoids are differentiated according to clinical spectrum, toxicity, and pharmacokinetics, such that the lack of response to a retinoid by a disease does not imply the same results with other retinoids.



**Figure 1.** Severe local reaction (erythema, edema, and blistering) in the area where 0.1% alitretinoin gel was applied.



**Figure 2.** Residual hyperpigmentation after 5 months of treatment with 0.1% alitretinoin gel.

**Table 1.** Treatment of Kaposi Sarcoma

Local	Systemic	Experimental
Surgery: Cryosurgery Laser Excisional	Chemotherapy: First-line: liposomal anthracyclines Second-line: paclitaxel	Hormones: hCG
Radiotherapy: X-rays Electron beam	Biological response modifiers: Interferon- $\alpha$	Retinoids: alitretinoin
Intralesional Injections: Vinblastine Vincristine Interferon	Antivirals: Antiretrovirals: HAART Anti-HHV8: ganciclovir, foscarnet	Angiogenesis inhibitors: Thalidomide, TNP-470, IM-862 Tecogalan Metalloproteinase inhibitors

Abbreviation: HAART, highly active antiretroviral therapy.

Alitretinoin, or 9-*cis*-retinoic acid, is a first-generation monoaromatic retinoid with the molecular structure shown in Figure 3.

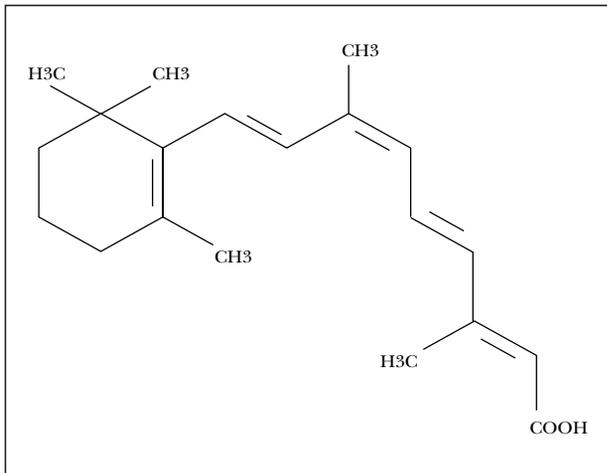


Figure 3. Molecular structure of alitretinoin.

The retinoid action is mediated by multiple pathways and results in complex inhibition or activation of a large number of genes regulated in a coordinated manner. This stimulates hormone response elements by a direct mechanism, inducing cell differentiation, while acting indirectly on genes that do not have these hormone response elements, leading to a decrease in proliferative and inflammatory activity. These biological effects probably depend on the selective mechanism acting on the various receptors.<sup>3</sup>

Alitretinoin is capable of binding to all retinoid receptors known to date (RAR and RXR), promoting apoptosis (acting on RXR) and cell differentiation (acting on RAR) while also decreasing cell proliferation (acting on RAR)<sup>3</sup> (Figure 4).

In 1999, the alitretinoin gel formulation was approved by the FDA for the local treatment of cutaneous lesions in patients with AIDS-related KS when the lesions are not ulcerated or lymphomatous, no visceral treatment is required, there is no response to highly active antiretroviral therapy (HAART), and/or RT or CT is not appropriate. However,

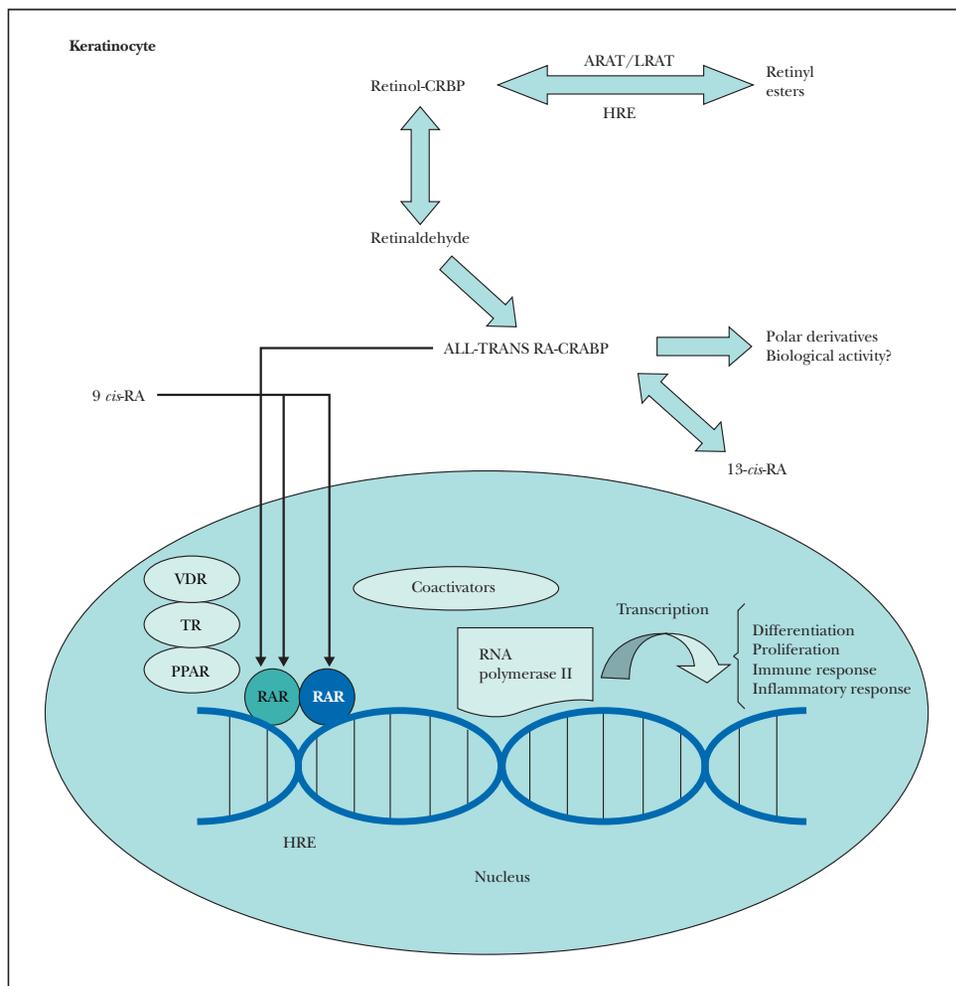


Figure 4. Representation of the mechanism of retinoids on the respective intracellular receptors. Abbreviations: ARAT, acyl-CoA:retinol acyltransferase; CRBP, cytosolic retinoic acid-binding protein; CRBP, cellular retinol-binding protein; HRE, hormone-response elements; LRAT, lecithin retinol acyltransferase; PPAR, peroxisome proliferation activated receptor; RA, retinoic acid; RAR, retinoic acid receptor; REH, retinyl ester hydrolase; RXR, retinoid X receptor; TR, thyroid receptor; VDR, vitamin D3 receptor. Modified from Bologna J, et al. *Dermatology*. 1st ed. Elsevier Mosby; 2004: Vol. II.

in the literature review we found a case of classic KS successfully treated over 7 months with 0.1% topical alitretinoin gel.<sup>4</sup>

Surgical treatment for our patient was ruled out because of the extent of the lesions, and chemotherapy was not considered due to associated substantial morbidity and advanced age. Because of the toxicity produced by the various treatments received (IFN- $\alpha$ -2b and electron beam radiotherapy), the patient was started on 0.1% alitretinoin topical gel, which caused a severe local reaction. This required a decrease in the frequency of application to once every 48 to 72 hours, with the formation of vesicles and blisters that finally resolved to leave residual hyperpigmentation.

Alitretinoin should be generously applied to the target lesions, while avoiding contact with the surrounding healthy skin. Initially, 2 applications are given per day, but this should be gradually increased (every 2-3 weeks) to between 3 and 4 applications a day, unless irritation occurs, in which case treatment should be decreased or discontinued until resolution and then resumed, provided there is no tissue necrosis. The degrees of irritation are summarized in Table 2.

The efficacy of 0.1% alitretinoin gel has been assessed in HIV-positive adult patients with KS confirmed by biopsy in various clinical trials, in accordance with the criteria for topical treatment of cutaneous KS proposed by the AIDS Clinical Trials Group. A response rate of 35% to 37% was observed; of the responses, 1% to 2% were complete and 34% to 35% were partial.<sup>1-3</sup> It has also been found that this response did not depend on ethnic group, Karnofsky score, number/area of lesions, CD4 lymphocyte counts, number of opportunistic infections, AIDS diagnosis, or previous therapy with CT or HAART.<sup>1-3</sup>

In general, the gel is well tolerated and the adverse effects are reversible, appearing only at the site of application: rash (77%), pain (34%), pruritus (11%), flaking (9%), and

**Table 2.** Grading of Alitretinoin-Induced Irritation

	<i>Erythema</i>	<i>Edema</i>	<i>Blistering</i>	<i>Necrosis</i>
0	-	-	-	-
1	+	-	-	-
2	+	+	-	-
3	++	+	+	-
4	++	++	++	+

edema/others (8%), all usually related to the duration of treatment and the frequency of applications.<sup>1-3</sup>

### Conflicts of Interest

The authors declare no conflicts of interest.

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