

# RETINOIDS IN SKIN CANCER CHEMOPROPHYLAXIS AND TREATMENT

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## 1. OVERVIEW OF SKIN CANCER

Skin cancer is the most common type of cancer in the United States. There are 2 main types of skin cancer: melanoma and non-melanoma. The 2 most common types of non-melanoma skin cancer are called basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Some other less common non-melanoma cancers including cutaneous T lymphoma (CTCL), Kaposi sarcoma (KS),...<sup>1</sup> Factors that increase the risk of skin cancer include ultraviolet radiation, skin type, gene factor, virus infection, immunodeficiency, and chemical substance,... Among them, ultraviolet radiation is one of the most emphasized factors.

## 2. OVERVIEW OF RETINOIDS

Retinoids include vitamin A (retinol) and its natural derivatives (retinaldehyde, retinoic acid, retinyl esters) as well as a large number of synthetic derivatives. Retinoids are required for

a large number of biological processes in the body. In particular, it has a role in embryogenesis, reproduction, vision, growth, inflammatory response, differentiation, growth, and apoptosis. Retinoids are present in keratinocytes in two forms, retinol and retinyl ester, of which retinyl ester is the major storage form. Retinoids act on many cellular processes, such as cell growth and differentiation, cell surface turnover, and immune regulation, via receptors in the cytoplasm and in the nucleus.

Retinoids' receptors in the cytoplasm include Cellular Retinoic Acid Binding Protein (CRABP) types I and II, and Cellular Retinol Binding Protein. The receptors in the nucleus include two groups of RAR (Retinoic acid receptor) and RXR (Retinoic X receptor). RAR exists in 3 forms RAR- $\alpha$ , RAR- $\beta$ , and RAR- $\gamma$ , of which RAR- $\gamma$  accounts for 90%, which is activated by all-trans-retinoic acid specific to RAR (tretinoin).

Based on structure and invention time, retinoids are divided into 4 generations (Figure 2.1).

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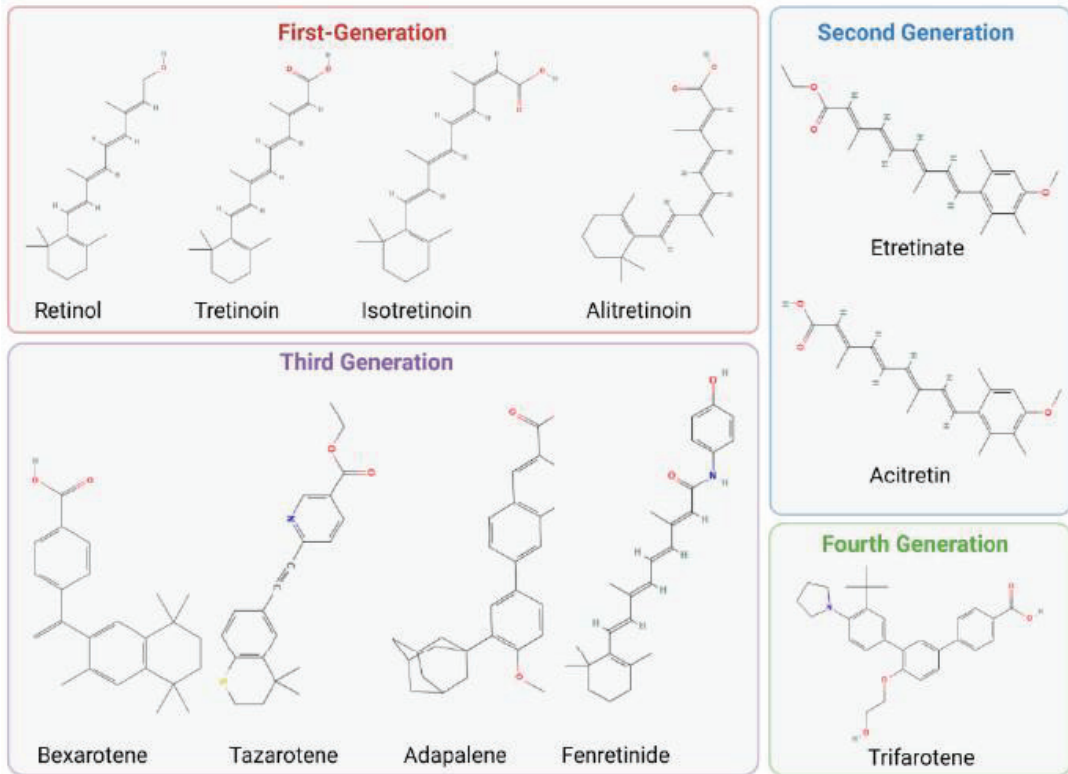
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Received 28 June 2023

Revised 26 September 2023

Accepted 29 November 2023

DOI: <https://doi.org/10.56320/tcdlhvn.42.138>



**Figure 1. Retinoids generations<sup>2</sup>**

The effect of retinoids on the skin demonstrates its role in the prevention and treatment of skin cancer including: control of keratinization and epidermal turnover, regulation of the immune chain reaction in the skin, regulation of blood vessel proliferation.<sup>2</sup>

Retinoids at physiological concentrations inhibit proliferation and regulate keratinization. Pharmacological doses of retinoids are shown to promote proliferation and epidermal thickening, inhibit squamous cell differentiation programs and cornification and promote apoptosis.<sup>3</sup> Therefore retinoids are used in keratosis disorders, KC and other cancers and their precursor lesions, for example: BCC, SCC, AK, Bowen disease,...

Retinoids are responsible for regulating cutaneous innate immune effectors, such as dendritic cells and Langerhans cells.<sup>4</sup> Skin-

homing and skin resident T lymphocytes are also influenced by retinoids.<sup>5</sup> The immunomodulatory properties of retinoids can be highly beneficial for treating inflammatory skin conditions like acne, rosacea, and also skin cancers that involve T cells like CTCL,...

Retinoids not only alter cellular immunity in the skin but also assist in intrinsic immune defenses by controlling the replication of certain viruses. The presence of Human Papilloma Virus (HPV) is known to cause cSCCs by manipulating the E6 and E7 viral oncoproteins. Retinoid treatment can play a significant role in inhibiting the transformation process by repressing E6 and E7 transcription in HPV-16-infected keratinocytes.<sup>6</sup> Similarly, retinoids prevent the replication of KSHV, which is responsible for KS, in endothelial and epithelial cells in vitro.

Retinoids also play a crucial role in controlling vascularization within the dermis and hypodermis. They can help in reducing the expression and secretion of vascular endothelial growth factor (VEGF) by keratinocytes.<sup>7</sup> This mechanism leads to a decrease in dermal angiogenesis. Additionally, pre-treatment with ATRA can help attenuate the production of VEGF induced by UV exposure in keratinocytes. This effect is due to the downregulation of the MAPK/ERK pathway.

### **3. ROLE OF RETINOIDS IN SKIN CANCER PREVENTION AND TREATMENT**

#### **3.1. Skin cancer prevention**

Retinoids are used to prevent skin cancer in high-risk subjects. These subjects include those who have a history of developing multiple keratinocyte carcinomas (KCs), immunosuppressed patients, and those who have genodermatoses that predispose them to developing KCs. Retinoids have been shown to decrease the numbers of new KCs in high-risk individuals and have even been successfully used to treat some existing KCs. Retinoids work by promoting cellular differentiation and reducing cell proliferation, both of which play a critical role in the development and progression of skin cancer. Regular use of retinoids can help prevent the occurrence and recurrence of KCs in high-risk subjects. While retinoids are not currently FDA-approved specifically for the chemoprevention of keratinocyte carcinomas (KCs), there is substantial evidence indicating their effectiveness as prophylactic agents against skin cancer.

The use of acitretin and isotretinoin, for skin cancer prevention, specifically for the prevention of cutaneous squamous cell carcinoma (cSCC), is recommended in guidelines outlined by the

U.S. National Comprehensive Cancer Network (NCCN). In the NCCN guidelines for Squamous Cell Skin Cancer prevention, oral retinoids are recommended for patients who are at high risk for developing cSCC or actinic keratoses (AKs).<sup>8</sup>

Acitretin is the retinoid with the most evidence for skin cancer prevention in organ transplant patients. Bavinck et al. performed the first randomized placebo controlled trial assessing oral acitretin (30 mg/day) for the chemoprevention of KCs in renal transplant recipients. At the end of their study, conducted across 6 months, patients in the acitretin treatment arm had developed fewer KCs and premalignant lesions (AKs) compared to the placebo arm.<sup>9</sup> Another study assessed low-dose (0.2 mg/kg/day) acitretin for AK and KC chemoprevention in renal transplant patients.<sup>10</sup>

Retinoids can be useful for preventing skin cancer formation in patients receiving treatments that increase the risk of cancer. For example, oral retinoid use has been associated with a lower incidence of cSCC among patients who have received PUVA therapy for psoriasis. Additionally, patients with cancer-predisposing genodermatoses, such as xeroderma pigmentosum (XP), can benefit from retinoid chemoprevention.<sup>11</sup> Clinical trials have demonstrated that treatment with isotretinoin reduced the formation of basal cell carcinomas (BCCs) and SCCs in XP patients. Research results revealed that after discontinuing treatment with oral isotretinoin, tumor formation increased by 8.5 fold, underscoring the importance of ongoing preventive measures in high-risk individuals.<sup>12</sup>

#### **3.2. Skin cancer treatment**

Retinoids are effective treatments for some skin cancers, mainly non-melanoma cancer. Some indications are FDA-approved.



### 3.2.1. BCC treatment

Long-term use of tazarotene 0.1% gel has been found to be effective in treating 30% to 50% of sporadic basal cell carcinomas (BCCs). In a study by Duvic et al., the use of 0.1% topical tazarotene was investigated for the treatment of BCC tumors. The study found that almost 60% of tumors treated with tazarotene for 12 weeks had regressed prior to excision. Mild-to-moderate local side effects were reported, including crusting/scabbing, erythema, and ulcerations.<sup>13</sup> Despite the local side effects, tazarotene cream was deemed to confer an appreciable level of clinical benefit.

The combined use of acitretin and tretinoin also gives a positive effect. In addition, tretinoin 0,05% alone was also effective in reducing BCC lesions but often relapsed after stopping application. Oral isotretinoin is less effective, at high doses, or causes side effects. Etretinate helps to reduce the number and size of BCC lesions and photokeratosis, and reduce the expression of metabolic markers of BCC.

### 3.2.2. Actinic keratosis treatment

Various retinoids have been shown to be effective in the prevention and treatment of photokeratosis. The drugs used include: acitretin, etretinate, isotretinoin, adapalene, tretinoin,

retinaldehyde, etc. Some effective treatments are listed below:

- Acitretin: 10-50mg/d - 6 - 12 months
- Isotretinoin: 0.4-0.5mg/kg/d - 12 months
- Tretinoin: 0.05-0.1%, 3-15 months
- Adapalene: 0.1-0.3% - 6 months.<sup>14</sup>

### 3.2.3. SCC treatment

Similarly in the treatment of BCC, tazarotene 0.1% applied daily for 6 months on SCC lesions showed 100% of patients to have complete/partial response on clinical and histopathology.<sup>15</sup>

Early studies in the 1980s considered the use of oral isotretinoin for cSCC treatment, and it was found to be effective in a subset of patients with advanced disease at a dose of 1-2 mg/kg/day.<sup>16</sup> In a recent case report, oral acitretin was used in combination with clarithromycin to successfully treat cSCC in three patients.<sup>17</sup>

### 3.2.4. CTCL treatment

Oral or topical bexarotene 0.1 - 1% was approved by FDA for the treatment of CTCL in patients with advanced stage or failure of at least 1 prior systemic therapy.

In addition, some of the oral/topical retinoids used in the treatment of cutaneous T lymphoma are shown in the table below:

Dosages of Topical Medications

Retinoid	Dose
Bexarotene	Apply to lesions in increasing increments weekly: every other day, every day, twice daily, three times daily, four times daily
Tazarotene <sup>a</sup>	Apply to lesions daily
Alitretinoin <sup>a</sup>	Apply to lesions twice daily

<sup>a</sup> Case studies.

Dosages of Systemic Medications

Retinoid	Dose
Bexarotene	150–300 mg daily, can be increased to 400 mg daily for refractory cases
Isotretinoin	1–2 mg/kg daily
Acitretin	10–50 mg (mode: 25 mg) daily, titrated to 10 mg daily or 25 mg three times weekly for maintenance
Alitretinoin <sup>a</sup>	30 mg daily

<sup>a</sup> Case study.

**Table 2. Use of retinoids in CTCL treatment<sup>18</sup>**

### 3.2.5. Kaposi sarcoma treatment

Localized or non-progressive Kaposi sarcoma lesions are usually indicated for treatment by methods of excision, cryosurgery, topical treatment, etc. 0.1% alitretinoin gel has been FDA-approved for the treatment of AIDS-related KS. Additionally, 0.1% alitretinoin is being considered for off-label use in treating non-AIDS related Kaposi's sarcoma (KS), given its reported effectiveness.<sup>19</sup> Although not commonly used in clinical practice, oral acitretin has been successful in treating classic KS unrelated to HIV.<sup>19</sup>

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