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Journal of Dermatological Treatment

ISSN: 0954-6634 (Print) 1471-1753 (Online) Journal homepage: www.tandfonline.com/journals/ijdt20

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To cite this article: Samar Khalil, Tara Bardawil, Carla Stephan, Nadine Darwiche, Ossama Abbas, Abdul Ghani Kibbi, Georges Nemer & Mazen Kurban (2017) Retinoids: a journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects, Journal of Dermatological Treatment, 28:8, 684-696, DOI: 10.1080/09546634.2017.1309349

To link to this article: https://doi.org/10.1080/09546634.2017.1309349

Published online: 02 Apr 2017.

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JOURNAL OF DERMATOLOGICAL TREATMENT, 2017
VOL. 28, NO. 8, 684–696
http://dx.doi.org/10.1080/09546634.2017.1309349

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REVIEW ARTICLE

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Retinoids: a journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects

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ABSTRACT

Retinoids are a class of compounds derived from vitamin A or having structural and/or functional similarities with vitamin A. They are classified into three generations based on their molecular structures. Inside the body, retinoids bind to several classes of proteins including retinoid-binding proteins and retinoid nuclear receptors. This eventually leads to the activation of specific regulatory regions of DNA – called the retinoic acid response elements – involved in regulating cell growth, differentiation and apoptosis. Several clinical trials have studied the role of topical and systemic retinoids in disease, and research is still ongoing. Currently, retinoids are used in several fields of medicine. This paper aims to review the structure, mechanisms of action, and adverse effects of retinoids, as well as some of their current uses in Dermatology.

ARTICLE HISTORY
Received 31 January 2017
Revised 26 February 2017
Accepted 26 February 2017

KEYWORDS
Retinoids; retinoic acid; isotretinoin; acne vulgaris; psoriasis

Introduction

Historical background

The term "Retinoids" refers to chemical compounds which are derivatives of vitamin A or all-*trans* retinol or synthetic compounds that share structural and/or functional similarities with the vitamin. The first medicinal use of vitamin A dates back to the 1500s BC as night-blindness or nyctalopia was treated with topical liver juices. It is now known that the liver is particularly rich in retinol and that only enteral or parenteral administrations of vitamin A are effective in treating nyctalopia. In 1913, McCollum and Davis were the first to identify vitamin A, a nutrient in egg yolk and butter necessary for the growth of rats (1). In 1925, Wolbach et al. found that vitamin A deprivation in mice leads to squamous metaplasia in several epithelial tissues of the body, atrophy of glands, and failure to store fat. In 1930, β-carotene was found to be a precursor of retinol *in vivo*. Later, in 1931, Karrer et al. determined the chemical structure of retinol. Isler and Huber succeeded in synthesizing this vitamin in 1947. Thereafter, several trials studied the role of retinoids in curing disease. In the 1970s and 1980s, many studies found that retinoic acid can halt carcinogenesis in several types of cancer including integumentary, gastrointestinal and genitourinary tumors (1). Currently, retinoids are widely used in several fields of medicine and ongoing research is still studying their undiscovered potential. This paper aims to review the structure, mechanisms of action, and adverse effects of retinoids as well as some of their current uses in Dermatology.

Structure, metabolites, and mode of action

Structure and metabolites

Vitamin A is a small hydrophobic molecule with three structural domains: a cyclic ring, a polyene side chain, and a polar end-group (Figure 1). It cannot be synthesized *de novo* by the human body. Its main dietary sources are plants with carotenoid pigments – such as sweet potatoes and carrots – and animals' livers. Once ingested, vitamin A is absorbed in the proximal part of the small intestine in association with chylomicra. Inside the body, vitamin A is converted into several metabolites called retinoids that differ mainly in their polar end-group: a hydroxyl in retinols, an aldehyde in retinals, a carboxylic acid in retinoic acids, and an ester in retinyl esters. Retinol is the main circulating form of the vitamin, retinyl ester is the storage form in the liver and retinoic acid is the main active metabolite. Retinoids are metabolized by the hepatic system and eliminated through the biliary or renal tracts (2). There are two main classes of receptors that bind to retinoids: retinoid-binding proteins and retinoid nuclear receptors (3).

Retinoid-binding proteins

Retinoid-binding proteins are necessary for the stabilization of hydrophobic retinoids in aqueous media (3). They can be divided into the plasma retinol-binding protein (RBP 4), the interstitial retinol-binding protein (RBP 3), and the cellular retinol-binding proteins (CRBPs or RBP 1, RBP 2, RBP 5, and RBP 7). RBP 4 is a single polypeptide chain belonging to the lipocalin superfamily of proteins. It is synthesized in the liver and transports vitamin A to its target tissues. The complex of RBP and retinol – called holoprotein – is bound to transthyretin, which stabilizes it further and prevents its filtration in the renal glomeruli. Deficiency of vitamin A decreases the secretion of RBP 4 and causes it to accumulate in the endoplasmic reticulum of hepatocytes.

Two cytoplasmic retinol-binding proteins (CRBP I and CRBP II) and two cytoplasmic retinoic acid-binding proteins (CRABP I and CRABP II) have been well characterized. CRBP I and CRBP II exhibit a high amino acid sequence homology but they have different tissue distributions. CRBP I is expressed in multiple tissues including

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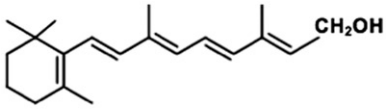
the liver, lungs, reproductive organs, brain, and eyes. CRBP II, on the other hand, is restricted to the small intestine and contributes to the absorption of the vitamin. CRABP are structurally similar to CRBPs but only bind to retinoic acid. Cellular retinal-binding protein (CRALBP) and the interphotoreceptor retinoid-binding protein (IRBP) are other cytoplasmic proteins found in the eye. They help mediate the visual function of retinal (3).

Retinoid nuclear receptors

Retinoid nuclear receptors belong to two families: the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs) which belong to the steroid/thyroid hormone receptor superfamily. These two families are divided into three isotypes each: α, β, and γ and have different ligand binding affinities. RARs bind to both all-*trans* and 9-*cis* retinoic acid, the two major naturally occurring vitamin A derivatives, whereas RXRs, only bind to 9-*cis* retinoic acid. Ligands that only bind to the RXRs are called rexinoids.

The two families of receptors exist together as a dimer. RARs heterodimerize with RXRs. RXRs can homodimerize or heterodimerize with several other families of receptors including RARs, the vitamin D3 receptor, the thyroid hormone receptor, as well as receptors for fatty acids and bile acids. Within these heterodimers, RXRs act either as silent or active partners. When RXRs are active partners, binding of the RXR ligands leads to a response. Therefore, retinoic acid can regulate the pathway mediated by the other receptor. For instance, retinoic acid can stimulate lipolysis and improve insulin sensitivity by activating a fatty acid receptor, peroxisome proliferator-activated receptors (PPARs). When RXR is a silent partner, binding of the RXR ligand does not lead to a response (4).

In the absence of ligands, RAR–RXR heterodimers are bound to corepressors which results in chromatin condensation and inaccessible DNA. Binding of retinoic acid leads to the dissociation of corepressors and subsequent binding of coactivators. The heterodimers then bind to specific DNA sequences found in the promoter region of retinoid-responsive genes, called the retinoic acid response elements (RARE). This leads to the activation or repression of genes responsible for regulating cell growth, differentiation and apoptosis (5). Some retinoid functions are mediated through RARE-independent genomic effects and through non-genomic effects (6).



Vitamin A
All Trans Retinol

Figure 1. The molecular structure of vitamin A.

Classification of retinoids

Retinoids are derived from the vitamin A molecule with substitutions occurring in all three of its structural domains. The first retinoid molecule, synthesized in 1955, is 13-*cis*-retinoic acid or isotretinoin. Since then, over two thousand retinoids have been synthesized. They are typically classified into three generations that will be discussed next. Some acknowledge a fourth generation of retinoids, those that are derived from pyranones.

First generation

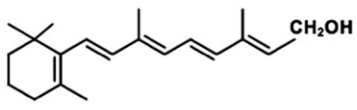
First generation retinoids are non-aromatic retinoids that are naturally occurring (Figure 2). These include retinol, retinal, isotretinoin (13-*cis* retinoic acid), tretinoin (all-*trans* retinoic acid), and alitretinoin (9-*cis* retinoic acid) among others. First-generation retinoids retain the cyclic structure of vitamin A with changes occurring in the polar end group and the polyene side chain (7).

Second generation

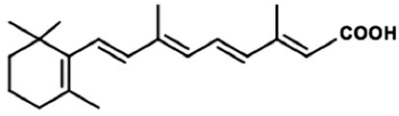
Second-generation retinoids are monoaromatic compounds formed by making changes to the cyclic ring of vitamin A (Figure 3). These include etretinate, acitretin, and motretinate. Their structures make them more lipophilic with a higher bioavailability than first generation retinoids. Acitretin is the active metabolite of etretinate and is orally bioavailable and has now replaced it in the treatment of various disorders. Acitretin contains a negatively charged side group rendering it less lipophilic than etretinate (8). Its mean half-life elimination is two days while the half-life of etretinate is 120 d. Some studies report that etretinate can still be detected in the subcutis more than two years after discontinuation of therapy. Moreover, acitretin can be converted to etretinate in the body especially when taken with ethanol. Therefore, female patients should abstain from drinking alcohol during therapy and for at least a couple of months after stopping acitretin (9).

Third generation

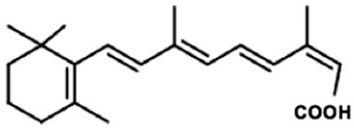
Third-generation retinoids are formed by cyclization of the polyene side chain (Figure 4). This group includes adapalene, tazarotene, and bexarotene which are polyaromatic molecules. Because of their structures which are more rigid than first- and second-



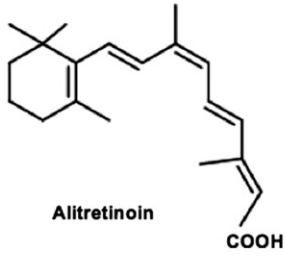
Retinol



Isotretinoin



Tretinoin



Alitretinoin

Figure 2. First-generation retinoids: retinol, tretinoin, isotretinoin, and alitretinoin.

generation retinoids, consequently third generation retinoids bind a narrower variety of receptors (7).

Side effects of retinoids

Topical

Topical retinoid therapy can lead to local skin irritation including dryness, peeling, erythema and pruritus. This is known as retinoid dermatitis or the "retinoid reaction". It is recommended to start with the lowest strength and frequency of application and then increase the treatment intensity as tolerance develops. Patients must be educated on the use of moisturizers as well as sunscreens. Many patients report a decreased tolerance to sunlight exposure while on therapy. Furthermore, ultraviolet light decreases the expression of retinoid receptors in the skin thereby decreasing their effectiveness (7,10).

Systemic

Adverse events of systemic retinoids are dose dependent. Mucocutaneous effects are common. Cheilitis is the earliest and most common side effect. Dryness of the oral mucosa can also occur. The nares may be involved leading to epistaxis. Xerophthalmia is believed to be due to the retinoid-induced meibomian gland dysfunction. Xerosis and fingertip fissuring can become quite bothersome. Hair loss, nail fragility, periungual granuloma, and paronychia are also seen. There have been some case reports of superimposed *S. aureus* infections in cases of severe cheilitis or retinoid dermatitis. In such patients, topical antibiotics are advised (11,12).

Systemic adverse effects of oral retinoid therapy are also well observed. Musculoskeletal effects include arthralgias, myalgias, and bony pain. Creatinine kinase levels may occasionally rise. Retinoids increase the number of osteoclasts at the periosteal side of cortical bones in both *in vivo* and *in vitro* murine models. Furthermore, some studies have shown that they inhibit cortical bone formation *in vivo*. Despite a clear impact of retinoids on bone metabolism at the molecular level, the long-term clinical effect on bone health is still unclear. Some studies report that excessive vitamin A intake is associated with decreased bone mineral density and increased risk of fractures, while other studies fail to show this effect and in some cases they even display bone protective effects. Other skeletal changes include premature fusion of the epiphyses, skeletal hyperostosis, and extraspinal calcification of ligaments and tendons (12,13).

Neurologic effects of retinoids include headaches which are usually mild in nature. Pseudotumor cerebri may rarely occur. Persistent headaches, visual impairment, or papilledema must raise the concern for increased intracranial pressure. Tetracyclines also increase the risk of pseudotumor cerebri; their combination with retinoids is, therefore, contraindicated (12). Retinoids can also lead to night blindness or nyctalopia by inhibiting 11-*cis*-retinol dehydrogenase. The latter is an enzyme of the visual cycle responsible for the formation of 11-*cis* retinal, the chromophore of rods and cones (14). If a patient is diagnosed with retinoid-induced pseudotumor cerebri or nyctalopia, the retinoid should be discontinued immediately.

Gastrointestinal effects including nausea, abdominal pain, and diarrhea are not commonly observed. Baseline fasting cholesterol

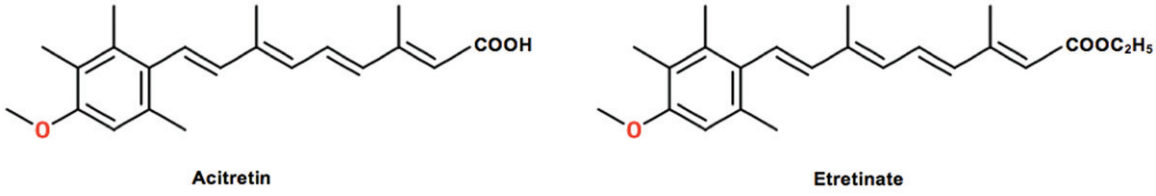


Figure 3. Second-generation retinoids: acitretin and etretinate.

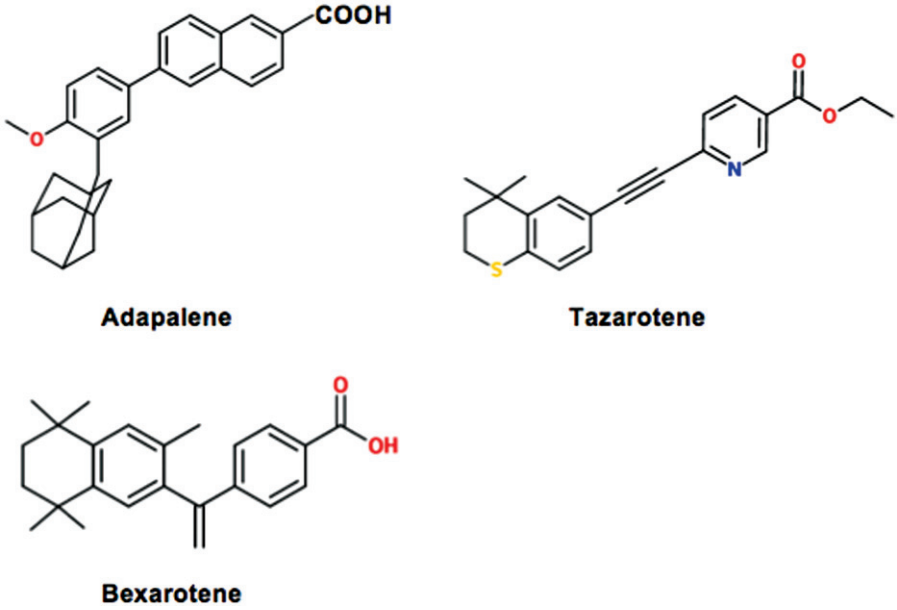


Figure 4. Third-generation retinoids: adapalene, tazarotene, and bexarotene.

levels, triglyceride levels, and liver function tests (LFTs) must be obtained before the initiation of therapy. Retinoids lead to an increase in the levels of triglycerides and total cholesterol and to a decrease in the high-density lipoprotein (HDL) levels. Liver enzymes typically rise between 2 and 8 weeks of therapy and return to normal levels within one additional month. Treatment should be discontinued in cases of transaminase increases of more than three-fold the upper normal limit (15). The frequency of blood testing varies depending on the country and the physician. A recent systematic review and meta-analysis showed that isotretinoin leads to an increase in lipid levels and LFTs from baseline (16). However, the proportion of patients with laboratory abnormalities is relatively low, and the mean changes in levels do not meet the criteria for high risk. The results of this study do not support monthly testing in patients without risk factors, but rather testing at baseline and the first 1 to 2 months after initiating therapy (16). If the blood tests are normal, no further testing may be needed. If the labs are abnormal, it is advisable to reduce the dose or, rarely, to discontinue therapy (17). It is recommended to avoid alcohol intake during therapy with any oral retinoid because of the increased risk of hepatic toxicity. Chronic alcohol ingestion is associated with increased hepatic metabolism of retinoids leading to the production of compounds with possible fibrogenic and toxic properties (18).

The greatest concern of oral retinoid therapy is the well-documented teratogenic effect. Oral retinoids are considered as category X by the United States (US) Food and Drug Administration (FDA). They result in neural-crest defects called retinoic acid embryopathy leading to abnormalities mainly of the central nervous system, face, heart, and thymus. In 2006, the US government initiated the iPledge, a program intended to prevent the use of isotretinoin in pregnant females. Similar precautions were also taken for acitretin, bexarotene, and alitretinoin. Women prescribed oral retinoids should be on two effective forms of contraception started one month before beginning of therapy. After retinoid therapy is discontinued, pregnancy should still be avoided for an additional one month with isotretinoin, alitretinoin, and bexarotene and 2–3 years with acitretin (19). Studies using topical retinoids failed to show a significant increase in the plasma concentrations of the drug even with excessive applications (20–22). Therefore, topical retinoids are unlikely to have any teratogenic effects. Nevertheless, physicians prefer to avoid them during pregnancy.

The effect of isotretinoin on depression and mood has long been a subject of debate. Post-marketing reports of depression and suicide associated with isotretinoin use for acne surfaced shortly after its approval by the US FDA in 1982. Thereafter, the manufacturer added a section about possible psychiatric adverse events in its product information. In the literature, there are multiple case reports about the association between isotretinoin and psychiatric symptoms including depression, irritability, aggression, suicidality, sleep disturbances, mania, and psychosis. Most commonly, the depression and suicidality manifested after 1–2 months of treatment. In many of these cases, these symptoms resolved or improved after the discontinuation of the retinoid and in some cases, they recurred with the reintroduction of the drug. Some of the larger-scale studies have also indicated an association between retinoid use and depression while others find no association and some even show a positive effect of the drug on mood. In general, the psychiatric literature suggests an association between the drug and depression while the dermatologic literature highlights the improvement in the depressive symptoms and self-image that accompanies acne treatment (23,24). Due to the limitations associated with earlier studies, larger placebo controlled trials are needed to sort this controversy. Meanwhile, physicians should closely monitor their patients for any mood changes while on therapy. The mechanism of action that relates isotretinoin to mood is still unclear. Retinoic acid may have effects in areas of the brain that are involved in depression namely the striatum, hippocampus, frontal cortex, and hypothalamus. Some studies show a reduction in the metabolism of the frontal cortex and in its blood flow during treatment. Retinoids could lead to a dysregulation in neurotransmission in the hippocampus and striatum, especially in the dopaminergic pathways. In the hypothalamus, they might alter the expression or the activity of the corticotropin-releasing hormone (CRH), a known player in the pathogenesis of depression (23,24). The retinoids side effects mentioned above are summarized in Table 1.

Clinical uses

The clinical uses of retinoids in Dermatology are summarized in Table 2.

Disorders of the sebaceous and apocrine glands

Retinoids have multiple effects that target acne vulgaris and related disorders. Topical retinoids are comedolytic and anticomedogenic. They normalize follicular keratinization and have immunomodulatory effects. They are, therefore, effective in the treatment of both inflammatory and non-inflammatory acne. It is also recommended to use them as maintenance therapy once acne lesions have cleared out because of their preventive properties. In addition to all these effects, systemic isotretinoin decreases sebum production, and inhibits P. acnes growth via changes in the follicular milieu. Therefore, isotretinoin targets all the steps in the pathogenesis of acne (25).

Table 1. Some side effects of systemic retinoid therapy.

System	Adverse effects
Mucocutaneous	Cheilitis
	Dryness of the oral mucosa
	Epistaxis
	Xerophthalmia
	Xerosis
	Fingertip fissuring
	Hair loss
	Nail fragility, periungual granuloma, paronychia
Musculoskeletal	Myalgias
	Arthralgias
	Bony pain
	Premature fusion of the epiphyses
	Skeletal hyperostosis
	Calcification of tendons and ligaments
Neurologic	Headaches
	Pseudotumor cerebri
Ophthalmologic	Nyctalopia
Gastrointestinal/ metabolic	Nausea
	Abdominal pain
	Diarrhea
	Elevation in liver function tests
	Elevation in serum triglycerides and cholesterol
Teratogenicity	Abnormalities of the central nervous system, face, heart, and thymus
Psychiatric	Depression
	Irritability/aggression
	Suicidality
	Sleep disturbances
	Mania
	Psychosis

Table 2. On and off label uses of retinoids in dermatology.

Disease	Retinoids used	Dose
Acne vulgaris	*Topical*	
	Adapalene	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
	Tazarotene	
	Tretinoin	
	Systemic	
	Isotretinoin	0.5–2 mg/kg/d for a total cumulative dose of 120–150 mg/kg
Rosacea	*Topical*	
	Adapalene	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
	Tazarotene	
	Tretinoin	
	Systemic	
	Isotretinoin	10 mg/d to 1 mg/kg/d
Hidradenitis suppurativa	*Systemic*	
	Acitretin	0.25–0.88 mg/kg/d
	Isotretinoin	0.5–1.2 mg/kg/d
Psoriasis	*Topical*	
	Tazarotene	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
	Systemic	
	Acitretin	25–50 mg/d
Pityriasis rubra pilaris	*Topical*	
	Tazarotene	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
	Tretinoin	
	Systemic	
	Acitretin	0.5 mg/kg/d (adult)
	Isotretinoin	1 mg/kg/d (adult)
Chronic hand eczema	*Systemic*	
	Alitretinoin	10–30 mg/d
Lichen planus	*Topical*	
	OLP	Thin layer over lesion two to four times daily
	Isotretinoin	
	Retinaldehyde	
	Retinoic acid	
	Tazarotene	
	Tretinoin	
	Systemic	
	CLP	
	Acitretin	30 mg/d
	OLP & NLP	
	Alitretinoin	30 mg/d
Ichthyosis	*Topical*	
	Adapalene	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
	Tazarotene	
	Tretinoin	
	Systemic	
	Acitretin	0.5 mg/kg/d (adult)
	Isotretinoin	1 mg/kg/day (adult)
Darier's disease	*Topical*	
	Tazarotene	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
	Adapalene	
	Tretinoin	
	Systemic	
	Acitretin	Around 35 mg/d
	Alitretinoin	Around 30 mg/d
	Isotretinoin	0.5–1 mg/kg/d
Aging/photoaging	*Topical*	
	Tretinoin	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
	Tazarotene	
Actinic keratosis	*Topical*	
	Adapalene	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
	Isotretinoin	
	Tretinoin	
	Systemic	
	Acitretin	20 mg/d for chemoprophylaxis of SCC in renal transplant patients
Squamous cell carcinoma	*Systemic*	
	Isotretinoin	1 mg/kg/d for size reduction
Basal cell carcinoma	*Topical*	
	Tazarotene (0.1% gel)	Thin layer over affected area once daily at bedtime (less frequently if not tolerated)
Cutaneous T-cell lymphoma	*Topical*	
	Bexarotene	Thin layer over affected area once daily, then increase to four times daily if tolerated
	Systemic	
	Bexarotene	300–400 mg/m^2/d
Kaposi sarcoma	*Topical*	
	Alitretinoin	Thin layer over lesion two to four times daily
Muir–Torre syndrome	*Systemic*	
	Isotretinoin	0.5–1.2 mg/kg/d

Acne vulgaris

Topical retinoids. Tretinoin, adapalene, and tazarotene are the three topical retinoids that are FDA approved for acne treatment in the US. A thin layer of retinoids is applied over the entire susceptible area once daily at bedtime or less frequently if not well tolerated. During the first few weeks of treatment, patients may experience a flare up of their acne which resolves later on. Topical retinoids enhance the penetration of other topical agents such as antibiotics. In inflammatory acne, combination therapy of a topical retinoid with an antibiotic is superior to antibiotic monotherapy.

Tretinoin was the first topical retinoid to be used for acne. Because of the cutaneous irritability associated with treatment, newer formulations have been developed. Retin-A Micro and Avita are composed of tretinoin microsphere and polymerized tretinoin, respectively. This allows the release of the retinoid in a slow manner (25). In the presence of light or oxidizing agents such as benzoyl peroxide, tretinoin degrades over time. Therefore, concomitant use of benzoyl peroxide and exposure to sunlight are not advised during therapy.

Adapalene was approved for the topical treatment of acne in 1996. Its three aromatic rings make it more stable than tretinoin. In fact, it can be used in the morning and in combination with benzoyl peroxide (26).

Studies comparing tretinoin with tazarotene showed that the latter is more effective with comparable tolerability (27,28). Adapalene has similar efficacy and better tolerability compared with tretinoin (29,30). Some studies found that adapalene has similar efficacy compared with tazarotene but better tolerability especially during the early stages of treatment (31–33). Other trials found that tazarotene is more effective (34,35).

Systemic retinoids. Oral isotretinoin was launched commercially in 1982. It is indicated for severe recalcitrant nodulocystic acne. It is also used when either of the following criteria is met: resistance to conventional therapy including systemic antibiotics, scar formation, and significant psychological impairment (36) Patients who are started on isotretinoin therapy must be educated on the possible acne flare that may result with initiation of therapy. In these cases, the patient may be started on oral antibiotics or steroids and the dose of isotretinoin may be changed (37). Typically, 1–2 months of therapy are required for an effect to be observable. The recommended daily dose is 0.5 mg/kg for the first month. The dose is then gradually increased to a maximum of 2 mg/kg. The total dose to be achieved over an average of 5 months is 120–150 mg/kg. Since the oral availability of retinoids is enhanced with food intake, it is advisable to ingest the pill after meals (25). Clearance of acne lesions may occur during therapy or, not uncommonly, after treatment discontinuation.

A study published in 2011 compared four different dosing regimens of isotretinoin in 120 patients for a total of 16 weeks: group A received 1 mg/kg/d, group B received 1 mg/kg every other day, group C received 1 mg/kg/d for 1 week every 4 weeks, and group D received 20 mg every other day (38). Group A performed better at 8 weeks. However, at the end of the 16 weeks of treatment, patients with mild acne had similar results in all groups. Those with moderate acne did better in groups A, B, and D. Those with severe acne did best in group A. As expected, side effects were more commonly seen and more severe in group A (38). Other studies have also shown that low and intermittent dosing regimens of isotretinoin are effective in mild to moderate acne (39,40).

Acne recurrence can happen after completion of oral isotretinoin therapy, mainly in the first year. The relapse rates reported in different studies vary from 10% to 60% depending on several factors that include treatment variations and patients' characteristics. Some studies have found that relapse is more likely to occur in patients below the age of 16 years, women versus men, patients with less than nodular acne, patients who took low-dose isotretinoin therapy, patients with a prolonged history of acne, females older than 25 at the onset of therapy, and patients with truncal acne (25). There is some evidence that high cumulative doses of isotretinoin may reduce the risk of relapse in patients with severe acne vulgaris. In a prospective study, 180 patients were divided to receive cumulative doses of either less than 220 mg/kg or more than 220 mg/kg (41). The low-dose group had a higher rate of relapse. Retinoid dermatitis was more common in the high-dose treatment group but none of the other adverse effects was significantly different between the two groups. This study, however, has multiple limitations and further studies are needed to confirm these results (41).

Rosacea

Topical retinoids. In a 2005 study, 55 patients with papulopustular rosacea were assigned to receive either topical adapalene gel 0.1% or topical metronidazole gel 0.75% for a total of 12 weeks (42). The adapalene group had a more significant reduction in the inflammatory papules. There were no significant changes in the scores of erythema and telangiectases. In the metronidazole group, a significant decrease in erythema was noted. Both adapalene and metronidazole produced a comparable reduction in the pustules (42). This suggests that topical retinoids might have an additive effect to topical metronidazole. Few years later, another study found that clindamycin and tretinoin combination gel did not lead to a statistically significant reduction in the inflammatory papulopustules (43). A reduction in the erythema and telangiectatic component was, however, noted (43). Because of their local adverse effects and the lack of large-scale studies, topical retinoids are not the preferred treatment.

Systemic retinoids. Oral isotretinoin is used in severe disease not responding to conventional treatment with topicals and oral antibiotics, especially in the age of increasing antimicrobial resistance. It seems to be mostly successful in papulopustular rosacea because of its anti-inflammatory properties but it is also effective in erythematotelangiectatic and phymatous rosacea. This has been attributed to its ability to decrease cutaneous blood flow and to suppress sebaceous glands (44).

Typically, doses of 0.5–1 mg/kg/d of isotretinoin are prescribed. However, several studies have found that lower doses – as low as 5 mg/d – are also effective and better tolerated especially for papules and pustules. Relapse is common once the oral isotretinoin is discontinued. More studies are needed to determine the optimal dose and treatment duration which would produce a clinically satisfying outcome while minimizing side effects and relapse rates. Hofer et al. showed that a continuous minimal dose of isotretinoin with a mean of 0.07 mg/kg/d improves the quality of life of patients with rosacea compared with untreated patients. Long-term monitoring and proper contraception in fertile women are necessary if such a regimen is adopted (45).

Hidradenitis suppurativa

Systemic retinoids. An article published in the British Journal of Dermatology in 2013, reviewed the different studies assessing the role of retinoids in *Hidradenitis suppurativa* (HS) (46). A significant response was defined as a reduction of $\geq$50% in the Sartorius score, improvement in quality of life of $>$50%, and a moderate response was defined as reductions $<$50%, or if stated so by the

authors. A total of seven articles evaluated the effect of oral isotretinoin (0.5–1.2 mg/kg/d) on a total of 174 patients. Significant improvement was noted in 18% of patients, moderate improvement in 17% and no response was observed in 64%. About 12% of patients relapsed within a couple of months after treatment discontinuation. A total of six papers assessed the role of either etretinate (0.35–1.1 mg/kg/d) or its metabolite acitretin (0.25–0.88 mg/kg/d) in 22 patients with HS. About 73% of patients improved significantly, 23% moderately, and 5% did not respond. Relapse occurred in 35% of patients after 6 months off therapy and in 47% of patients after 1 year. Acitretin seems to be more effective than isotretinoin likely due to its stronger inhibitory effect on keratinization (46). Some authors recommend the use of isotretinoin pre and post-operatively in patients with HS (47).

Psoriasis and inflammatory dermatoses

Retinoids can induce cell differentiation and inhibit cell proliferation. They also have immunomodulatory and anti-inflammatory properties. Studies have shown that retinoids exert a modulatory effect on T-cells and polymorphonuclear cells and modulate the expression of inflammatory cytokines (48,49).

Psoriasis

Topical retinoids. Tazarotene is approved in several countries for the treatment of localized stable plaque psoriasis. It is applied once daily in the evening. Two multicenter, double-blind, randomized studies compared the use of tazarotene cream in both the 0.05% and 0.1% formulations to placebo (50). A total of 1303 patients applied one of the creams once daily to all psoriatic lesions for 12 weeks. Compared with placebo, both treatment creams led to a more significant reduction in plaque elevation, scaling. This response was maintained during the 12-week follow-up period. Erythema was less responsive to treatment. The 0.1% cream was more effective than the 0.05% cream, but was more irritating (50). In one study, tazarotene 0.05% and 0.1% gels were compared with fluocinonide (51). At the end of the 12-week treatment period, both retinoid concentrations were as effective as the steroid in reducing plaque elevation. At follow-up 4 weeks after treatment discontinuation, the tazarotene group had lower rates of relapse (51). The addition of a steroid to tazarotene leads to a greater effect than retinoid monotherapy (52). The retinoid would have the added benefit of reducing skin atrophy induced by steroids. The combination of tazarotene with phototherapy is more effective than phototherapy alone (53,54). A study comparing calcipotriol to tazarotene found the former to be more effective than the 0.05% retinoid cream but equally effective to the 0.1% cream (55).

Tazarotene was also studied in palmoplantar psoriasis. A randomized controlled trial of 30 patients found that tazarotene 0.1% cream is as effective as clobetasol propionate cream 0.05% applied for 12 weeks (56).

Systemic retinoids. Etretinate was the first systemic retinoid to be used in 1972in psoriasis. Currently, acitretin is the only systemic retinoid that is FDA approved for the treatment of psoriasis. It is available as 10 mg and 25 mg capsules. The optimal dosage is between 25 and 50 mg daily. Lower doses are less effective and higher doses have more side effects. In some patients, the condition may worsen shortly after starting treatment and starts to improve thereafter. The maximal response is usually achieved after 3–6 months of therapy. Discontinuation of therapy does not lead to a rebound effect (48).

A recent systematic review on the efficacy and safety of oral retinoids in different psoriasis subtypes has found that retinoid monotherapy has limited efficacy in chronic plaque-type psoriasis (57). However, it has an add-on effect when used with other therapeutic modalities such as corticosteroids and UV therapy. Re-PUVA is an approach consisting of giving an oral retinoid in combination with phototherapy (58,59). It leads to a faster and more significant response than either monotherapies. It also decreases the amount of radiation needed, thereby reducing the risk of cancer. In pustular psoriasis, monotherapy is very effective and is considered first line therapy. Since acitretin is so far the only anti-psoriatic medication without immunosuppressive effects, it can be safely used in HIV-associated psoriasis and has proven efficacy. An open study involving 36 patients with moderate to severe nail psoriasis has found a mean reduction of 41% in the Nail Psoriasis Severity Index (NAPSI) (60). About 25% of the patients showed complete or almost complete clearing of the lesions while 11% had no response.

Pityriasis rubra pilaris

Topical retinoids. In a case report, a young woman with circumscribed pityriasis rubra pilaris (PRP) type IV was treated with daily topical tretinoin 0.05% (61). Improvement in pruritus and erythema was noted after 2 months of treatment and a 50% reduction in lesion size was observed after 6 months. In another similar case, there was no response after 2 months of treatment with topical tretinoin and the patient was lost to follow-up (62).

Systemic retinoids. Systemic therapy is used in more advanced cases where oral retinoids are first-line therapy. Acitretin is considered to be more effective than isotretinoin. A paper by Dickens reviewed the cases of 15 patients with PRP who received isotretinoin therapy with initial doses ranging from 40 to 80 mg/d. After 25 weeks of treatment, 10 patients had total clearing, three had partial clearing and two showed no response. In a case report, a 9-year old male with recently diagnosed adult-onset PRP was treated with acitretin 25 mg every other day (63). After 6 months, the lesions had completely resolved and acitretin was stopped. Recurrence did not occur after 1 year of follow up. The treatment was well tolerated by the patient, with the only side effect being mild dryness of the lips (63).

Chronic hand eczema

Systemic retinoids. Alitretinoin is approved in Europe for use in severe chronic hand eczema (CHE) not responding to potent topical steroids. The dose is 10–30 mg/d for 12–24 weeks. It is not recommended in patients less than 18 years of age. In several studies, alitretinoin used in patients with severe CHE resulted in a dose-dependent improvement, with some patients reaching complete clearance or almost complete clearance (49). Patients who relapsed responded well to a second course of treatment. In many cases, long-term intermittent courses are needed to control the disease. Most adverse events were mild to moderate in intensity and post-marketing surveillance revealed that alitretinoin was generally well tolerated (49).

Lichen planus

Topical retinoids. The World Workshop in Oral Medicine IV (2004) recommended the use of topical retinoids as second line for the treatment of oral lichen planus (OLP). A review published in 2013 summarizes the studies using topical retinoids for both keratotic and erosive OLP (64). Since the early 1970s, several studies showed the efficacy of these agents clinically, histologically, and

ultrastructurally. Side effects were mild and transient but many studies reported the recurrence of the disease shortly after discontinuation of the retinoid therapy. Kar et al. found that 0.05% tretinoin is more effective then 0.05% betamethasone dipropionate, whereas Buajeeb et al. (64) showed the superiority of 0.1% fluocinolone acetonide compared with 0.05% retinoic acid. Topical retinoids are not commonly used for cutaneous lichen planus (CLP). In one article, topical tretinoin 0.1% cream in combination with azelaic acid and twice-monthly chemical peels resulted in a dramatic response in a patient with lichen planus pigmentosus and facial dyspigmentation (65).

Systemic retinoids. Acitretin is the most studied oral retinoid in CLP. In a randomized controlled trial, acitretin used at 30 mg/d for 8 weeks in 65 patients with CLP was superior to placebo (66). Significant improvement or remission was noted in 64% of patients in the acitretin group compared with 13% in the placebo group (66). In a case report of a patient with palmoplantar lichen planus, 2 months of acitretin at a dose of 0.5 mg/kg/d resulted in a complete resolution of the lesions (67). In another article, 30 mg/d of alitretinoin was used in two patients with nail lichen planus (NLP) resistant to conventional treatment. It led to a noticeable improvement within 2–4 months of therapy. Pterygium was resistant to treatment (68). In one case report, a patient with oral, esophageal, nail, and cutaneous lichen planus resistant to conventional therapy was treated with 30 mg/d of oral alitretinoin. Therapy resulted in complete resolution of mucosal and skin lesions within 4 weeks and of nail lesions within 6 months. Relapse occurred 4 months after treatment discontinuation so the patient received a second course of the oral retinoid (69). In a prospective study of 10 patients with severe OLP, alitretinoin at 30 mg/d resulted in >50% reduction in disease severity in 40% of patients (70).

Disorders of epidermal differentiation and keratinization

Topical retinoids have keratolytic properties and the ability to induce differentiation. In addition to these effects, oral retinoids may increase the patient's ability to sweat, thereby, decreasing overheating. They also improve ectropion and pseudoainhum which are seen in certain subtypes of ichthyosis.

Ichthyosis

Topical retinoids. Topical tretinoin, adapalene, and tazarotene can all be used. They are usually combined with other topical keratolytics and lubricants before systemic treatment is considered.

Systemic retinoids. Most ichthyoses, except for Netherton, respond well to systemic retinoids within a few weeks. Because of their many side effects, their use is typically delayed until the severity of the physical and/or emotional burden is beyond the patient's capability. Isotretinoin and acitretin are typically used. Acitretin is more effective in the palmoplantar area but isotretinoin has a lower half-life and is, therefore, it is preferred in women of childbearing potential. Low doses of isotretinoin are usually started and titrated up until a satisfactory response is achieved. About 1 mg/kg/d of isotretinoin or 0.5 mg/kg/d of acitretin is typically enough.

Autosomal recessive congenital ichthyosis (ARCI) is a form of non-syndromic ichthyosis. It includes lamellar ichthyosis (LI), congenital ichthyosiform erythroderma (CIE), and harlequin ichthyosis (HI). Several studies have proven the efficacy of oral retinoids in ARCI. However, this effect only lasts as long as treatment is maintained.

In a study evaluating the effect of acitretin therapy on seven patients with LI, two patterns of response were observed: some patients responded to gradually increasing doses of the oral retinoid (≥35 mg/d). The remaining did well with low doses (10–25 mg/d) and experienced worsening of their skin condition with higher doses. One patient who was suffering from severe alopecia experienced some hair regrowth after 4 years of treatment.

Harlequin ichthyosis is a severe variant of ARCI. Affected newborns are surrounded by a shell of profoundly thick scale. Mortality rates are high and are usually due to respiratory failure or fulminant sepsis. Several case reports have shown that early introduction of oral retinoids may prolong survival. Treatment duration is variable and long-term therapy is not always needed. In a review of 45 cases of HI, 24 babies were treated with an oral retinoid (isotretinoin, etretinate, or acitretin) with doses ranging between 0.5 and 2.5 mg/kg/d (71). About 83% of treated patients survived, while 76% of untreated patients died. About 63% of these deaths occurred within 3 d of birth. Among newborns who took retinoid therapy, half did not start treatment until after the age of 3 d. Therefore, others factors must have contributed to the early deaths among the non-treated group (71).

Epidermolytic hyperkeratosis (EH) is another form of ichthyosis characterized by severe blistering. Oral retinoids can first exacerbate the blistering. Therefore, it is important to start with low doses. In one study, four patients received a daily dose of 1.5 mg/kg of an aromatic retinoid for 3 weeks (72). The dose was then slowly tapered to 0.3 mg/kg/d and treatment was continued for a period of 3–5 months. After 1 month of therapy, palms and soles looked almost normal. Patients experienced thermal sensitivity in those areas for the first time. But when they got back to their jobs, they noticed an increased vulnerability of their new skin and, eventually, all decided to discontinue therapy (72).

Darier's disease

Topical retinoids. Topical isotretinoin was effective in several patients with localized and generalized Darier's disease (73). However, skin irritation was severe in some patients. Topical tazarotene had mixed efficacy, showing improvement in some patients but no response in others. A few case reports reported the efficacy of Adapalene in the treatment of localized Darier's disease (73). In one case report, topical tretinoin 0.1% applied twice daily for 1 month led to a significant response (74).

Systemic retinoids. Systemic retinoid therapy is used in severe disease refractory to other therapies. Long-term treatment is needed to maintain remission. Many patients experience an exacerbation of their disease when beginning therapy. It is, therefore, recommended to begin at low doses and then increase the doses gradually. Isotretinoin, alitretinoin, etretinate, and acitretin have all been studied in Darier's disease (74).

In one study, 17 out of 18 patients Darier's disease receiving etretinate therapy showed improvement of their disease with nine reaching near complete remission (75). Improvement began to appear within 2 weeks both clinically and histologically. Three patients also reported that their disease no longer exacerbated with sunlight exposure. One patient experienced exacerbation of his disease (75). Acitretin was given to five patients with Darier's disease at an initial dose of 35 mg/d. One month later, the dose was adjusted based on the response and side effects. After several months of treatment, improvement was noted in all patients with near total clearance in two patients (76).

A multicenter study enrolled 104 patients with Darier's disease to study the effects of systemic isotretinoin therapy (77). A starting dose of 0.5 mg/kg/d was used and the dose was increased weekly. Improvement in the lesions was observed within 1 month of treatment in the majority of patients. However, after treatment discontinuation, most lesions returned to that of pretreatment quality (77). Other articles have shown that alitretinoin 30 mg/d is effective in the treatment of Darier's disease (78,79).

Aging/photoaging

The efficacy of retinoids in photoaging was first demonstrated by Kligman et al. in 1984 and since then, retinoids have been considered a gold standard in the prevention and treatment of the photoaging skin. Retinoid treatments lead to epidermal thickening, increased collagen production, decreased collagen destruction, increased elastin and fibrillin, decreased epidermal melanin content, increased angiogenesis, and decreased atypia. This is clinically manifested by a smoother skin with less wrinkles, more homogeneous pigmentation and better elasticity (7).

Topical retinoids

Currently both tretinoin and tazarotene are approved for the treatment of the photoaging skin. Several weeks or months of treatment are needed before any changes become observable. A meta-analysis of 12 studies assessed the effect of tretinoin therapy in individuals with mild to severe photodamaged skin (80). In terms of fine wrinkles, tretinoin cream concentrations of 0.02% or higher were needed to have an effect superior to placebo. Minimal concentrations of 0.01% were required for coarse wrinkles, 0.025% for mottled hyperpigmentation, and 0.05% for actinic lentigines of the face. Only one study investigated actinic lentigines on the forearm and found that tretinoin 0.01% was superior to placebo (80).

A double-blind study by Kang et al. in 2001 compared different concentrations of tazarotene (0.01%, 0.025%, 0.05%, and 0.1%) to placebo applied topically once in the evening for 24 weeks in 349 subjects. All concentrations of tazarotene – except 0.025% – showed a statistically beneficial effect on fine wrinkling which increased with higher concentrations. Only 0.1% tazarotene had a significant effect on mottled hyperpigmentation. All concentrations were effective according to the investigator's assessment of overall improvement in photodamage.

A double-blind study by Lowe et al. compared tazarotene 0.1% cream with tretinoin 0.05% emollient cream applied once daily for 24 weeks in 173 individuals. During the course of treatment, tazarotene was superior in terms of mottled hyperpigmentation, coarse wrinkling, and overall assessment of the investigators. At the study endpoint, tazarotene was superior only in terms of fine wrinkling. The study conducted by Kang et al. in 2001 also compared the different concentrations of tazarotene to 0.05% tretinoin. At the end of 24 weeks of therapy, tazarotene concentrations of 0.05% and higher were as effective as tretinoin in terms of fine wrinkling, mottled hyperpigmentation, and physician assessed overall improvement. The lower tazarotene concentrations were somehow less effective but statistical significance was only reached with 0.025% tazarotene in terms of fine wrinkling (7).

Systemic retinoids

Systemic retinoids are not indicated for the treatment of photoaging. However, some studies have demonstrated the efficacy of low-dose systemic retinoids. In one study, patients received 10–20 mg of isotretinoin three times per week for 3 months (81). A clinical improvement in the overall effects of photoaging was observed and increases in the epidermal thickness and in the number of collagen fibers were noted (81). Another study by Bagatin et al. compared oral isotretinoin to topical retinoic acid (82). Patients received either 20 mg/d of isotretinoin or 0.05% of topical retinoic acid applied once daily for 6 months. Both therapies were found to improve the damages of photoaging causing an increase in epidermal thickness and a reduction in elastosis. However, isotretinoin was not found to be superior to retinoic acid (82).

Pre-malignant and malignant lesions

The role of retinoids in cancer prevention and treatment is widely recognized. They induce cell differentiation, inhibit cell proliferation, and induce apoptosis. Furthermore, many premalignant and malignant lesions are associated with aberrant expression of the retinoid receptors (83).

Actinic keratosis

Topical retinoids. Topical retinoids are not currently FDA approved for the treatment of actinic keratosis (AK) (84). However, multiple studies have shown their efficacy. A study by Alizerai et al. evaluated the use of topical 0.1% isotretinoin versus placebo applied twice daily for 24 weeks. The retinoid led to a significant reduction in the size of AK lesions on the face. No effect was noted on scalp or upper extremity lesions. Euvrard et al. demonstrated a significant reduction in AKs with adapalene 0.3% and 0.1%. Bollag et al. (84) demonstrated the efficacy of tretinoin 0.1% and 0.3% on AKs of the arms and hands.

Squamous cell carcinoma

Topical retinoids. In a randomized control trial, topical application of 0.1% tretinoin daily for more than a year showed no effect on the reduction of the risk of squamous cell carcinoma (SCC) (85). Currently, topical retinoids are not recommended for the chemoprevention of SCC.

Systemic retinoids. One study demonstrated the efficacy of isotretinoin at a dose of 1 mg/kg/d in reducing the size of SCC lesions refractory to radiation therapy and surgery (86). Systemic retinoids also seem to have a preventive effect in patients at an increased risk for SCC. Studies have shown that retinoid therapy reduced the risk of SCC in patients who received psoralen-UVA treatment for psoriasis or those taking BRAF inhibitors for the treatment of malignant melanoma (87,88).

Basal cell carcinoma

Topical retinoids. Tazarotene has been proposed for the treatment of basal cell carcinoma (BCC). In one study, 0.1% tazarotene gel was applied daily to 154 small superficial and nodular BBCs (89). After 24 weeks of treatment, 71% of the BCCs showed significant clinical and dermoscopic regression. About 30% healed without recurrence after 3 years of follow-up. Keratotic BCC was the major non-responsive type of BCC (89).

Systemic retinoids. In one study, three patients with multiple BCC were treated with oral isotretinoin for 2.5–4 years (90). Nine out of 65 lesions showed complete clinical regression. In one patient, some of the tumors enlarged slightly. No new lesions were detected in any of the three patients (90). Another study assessed the role of isotretinoin in chemoprevention of BCC. Patients who

previously had BCC were given either low-dose isotretinoin (10 mg/d) or placebo for 3 years (91). There was no difference in the occurrence of new BCC in both treatment groups.

Transplant patients

Solid organ transplant recipients (SOTR) have an increased risk of skin cancers. Intensive surveillance and proper treatment are necessary. Several studies report a beneficial effect of retinoids in cancer chemoprevention in SOTR.

Topical retinoids. A statistically significant reduction in the pre-existing AK was observed in two out of three studies assessing the role of topical adapalene in SOTR. No studies assessed the role of topical retinoids in chemoprevention.

Systemic retinoids. A study was conducted involving 13 renal transplantation patients with AK each receiving 20 mg/d of acitretin for 1 year (92). All patients experienced a significant reduction in the size of AK lesions. Histologically, an increase in the number of Langerhans cells was found as well as restoration of the keratinocyte architecture. Due to the risk of progression from AK to SCC, systemic retinoid therapy is recognized as a form of chemoprophylaxis of SCC in this population group (92).

Four different studies have shown a beneficial effect of etretinate on the development of new skin cancers in SOTR (93). A randomized controlled trial showed a significant reduction in the incidence of skin cancers in patients treated with 30 mg/d of acitretin (93).

Cutaneous T-cell lymphoma

Topical retinoids. Bexarotene is the only FDA-approved retinoid for the treatment of patients with cutaneous T-cell lymphoma (CTCL). It is available as a gel in a 1% formulation and as 75 mg gelatin capsules. The gel form is used for early stages refractory to other topical therapies. In a phase III clinical trial by Heald et al., topical bexarotene gel showed a response in patients with refractory or persistent early-stage CTCL (94). The FDA recommends the application of the gel once daily for the first week and then more frequently –- up to four times daily – if well tolerated. Treatment can induce erythema at the site of application and this is often confused with worsening disease.

Systemic retinoids. The bexarotene capsule form is used in patients with more generalized skin involvement who failed at least one other systemic therapy. The initial dose recommended by the FDA is 300 mg/m^2/d. If there is no response after 8 weeks, the dose can be increased to 400 mg/m^2/d. Some physicians prefer to start with a lower initial dose of 150 mg/m^2/d.

In a retrospective study published by Abbott et al. (95), bexarotene was used in 40 patients with MF and 26 patients with SS with a starting dose of 150–300 mg/m^2/d. Nineteen patients had early stage MF (IB–IIA) refractory to skin-directed treatment and 47 patients had advanced CTCL (IIB–IVB). Twenty-eight patients were treated with bexarotene monotherapy and the remainder were given additional treatment. Fifty-two patients completed a full month of treatment. Among those, six patients (9%) had a complete response, 23 (35%) had a partial response, 15 (23%) had stable disease, and eight (12%) had progressive disease (95). Another retrospective study compared tretinoin (RAR-specific) with bexarotene (RXR-specific) in the treatment of CTCL (96). There were no statistical differences in response rates, response duration or median survival in both treatment groups (96).

Systemic bexarotene causes hypothyroidism by several mechanisms: it reduces TSH-β mRNA levels, suppresses the secretion of TSH from thyrotrophs, and stimulates the peripheral metabolism of thyroid hormones (97). Therefore, it is recommended to start levothyroxine simultaneously with bexarotene. The current recommended dose of levothyroxine is 50 μg/d. Free T4 should be measured once weekly during the first 5–7 weeks of treatment, then once every 1–2 months. The dose of levothyroxine is then adjusted accordingly (97). Hypertriglyceridemia is another common side effect of bexarotene therapy and co-administration of fenofibrates is often required. The United Kingdom Cutaneous Lymphoma group recommends starting fenofibrate at 160–200 mg/d 1 week before initiating bexarotene therapy in all patients without contraindications, regardless of their baseline triglyceride levels (98). Interestingly, oral bexarotene is currently being evaluated for the treatment of Alzheimer's disease (99).

Kaposi sarcoma

Topical retinoids. In 1999, the FDA approved alitretinoin gel for use in AIDS-related kaposi sarcoma (KS). Alitretinoin is available as a 0.1% gel. The recommended frequency of application is twice daily initially to be increased later to four times daily if tolerated. In a randomized controlled trial of 268 patients with KS, alitretinoin 0.1% gel was superior to placebo (100). The minimum time to response was 14 d.

Muir–Torre syndrome

Systemic retinoids. In 1985, Spielvogel et al. (101) reported two cases with Muir–Torre syndrome. The first is a lady with a relevant familial history and a facial keratoacanthoma (KA) with multiple sebaceous lesions. A 20-week course of isotretinoin at a dose of 1.2 mg/kg/d resulted in a complete resolution of the KA and a decrease in the size of the sebaceous lesions. Recurrence occurred after treatment discontinuation and the patient received another course of isotretinoin and was eventually kept on a maintenance dose of 0.2 mg/kg/d. In the second case, 2 weeks of 0.5 mg/kg/d of isotretinoin followed by 3 months of 0.1 mg/kg/d resulted in a complete resolution of a sebaceous neoplasm of the chest. In both cases, no new lesions appeared while on treatment (101). The benefit of isotretinoin in Muir–Torre syndrome was reported in two other case reports (102,103).

Acknowledgements

Figures were created using the software eMolecules at www.emolecules.com.

Disclosure statement

None of the authors have any conflict of interest to disclose. There is no funding source. The article does not contain any studies with human participants or animals performed by any of the authors and thus there was no need for informed consent.

References

1. Wolf G. A history of vitamin A and retinoids. FASEB J. 1996;10:1102–7.
2. Harrison EH. Mechanisms involved in the intestinal absorption of dietary vitamin A and provitamin A carotenoids. Biochim Biophys Acta. 2012;1821:70–7.
3. Noy N. Retinoid-binding proteins: mediators of retinoid action. Biochem J. 2000;348:481–95.
4. Bushue N, Wan YJ. Retinoid pathway and cancer therapeutics. Adv Drug Deliv Rev. 2010;62:1285–98.

5. Bastien J, Rochette-Egly C. Nuclear retinoid receptors and the transcription of retinoid-target genes. Gene. 2004; 328:1–16.
6. Blomhoff R, Blomhoff HK. Overview of retinoid metabolism and function. J Neurobiol. 2006;66:606–30.
7. Mukherjee S, Date A, Patravale V, et al. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interv Aging. 2006;1:327–48.
8. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. J Am Acad Dermatol. 1998;39:S25–S33.
9. Briggs GFR, Yaffe S. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 9th edition. Philadelphia (PA): Lippincott Williams & Wilkins; 2012. p. 16–18.
10. Andersson E, Rosdahl I, Torma H, Vahlquist A. Differential effects of UV irradiation on nuclear retinoid receptor levels in cultured keratinocytes and melanocytes. Exp Dermatol. 2003;12:563–71.
11. Moy A, McNamara NA, Lin MC. Effects of isotretinoin on meibomian glands. Optom Vis Sci. 2015;92:925–30.
12. Saurat JH. Side effects of systemic retinoids and their clinical management. J Am Acad Dermatol. 1992;27:S23–S8.
13. Henning P, Conaway HH, Lerner UH. Retinoid receptors in bone and their role in bone remodeling. Front Endocrinol. 2015;6:31.
14. Golczak M, Maeda A, Bereta G, et al. Metabolic basis of visual cycle inhibition by retinoid and nonretinoid compounds in the vertebrate retina. J Biol Chem. 2008; 283:9543–54.
15. Sorg O, Kuenzli S, Saurat JH. Side effects and pitfalls in retinoid therapy. In: Vahlquist A, Duvic M, eds. Retinoids and Carotenoids in Dermatology. Vol. 39; 2007. p. 225–48.
16. Lee YH, Scharnitz TP, Muscat J, et al. Laboratory monitoring during isotretinoin therapy for acne: a systematic review and meta-analysis. JAMA Dermatol. 2016;152:35–44.
17. Altman RS, Altman LJ, Altman JS. A proposed set of new guidelines for routine blood tests during isotretinoin therapy for acne vulgaris. Dermatology (Basel). 2002;204:232–5.
18. Seitz HK. Alcohol and retinoid metabolism. Gut. 2000; 47:748–50.
19. Cunningham FG. Williams Obstetrics, 24 ed. New York: McGraw-Hill Education; 2014.
20. Chen C, Jensen BK, Mistry G, et al. Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. J Clin Pharmacol. 1997;37:279–84.
21. Nohynek GJ, Meuling WJ, Vaes WH, et al. Repeated topical treatment, in contrast to single oral doses, with vitamin A-containing preparations does not affect plasma concentrations of retinol, retinyl esters or retinoic acids in female subjects of child-bearing age. Toxicol Lett. 2006;163:65–76.
22. Yu Z, Sefton J, Lew-Kaya D, et al. Pharmacokinetics of tazarotene cream 0.1% after a single dose and after repeat topical applications at clinical or exaggerated application rates in patients with acne vulgaris or photodamaged skin. Clin Pharm. 2003;42:921–9.
23. Bremner JD, Shearer KD, McCaffery PJ. Retinoic acid and affective disorders: the evidence for an association. J Clin Psychiatry. 2012;73:37–50.
24. Ludot M, Mouchabac S, Ferreri F. Inter-relationships between isotretinoin treatment and psychiatric disorders: depression, bipolar disorder, anxiety, psychosis and suicide risks. World J Psychiatry. 2015;5:222–7.
25. Gollnick H, Cunliffe W, Berson D, Global Alliance to Improve Outcomes in A, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol. 2003;49:S1–S37.
26. Martin B, Meunier C, Montels D, Watts O. Chemical stability of adapalene and tretinoin when combined with benzoyl peroxide in presence and in absence of visible light and ultraviolet radiation. Br J Dermatol. 1998;139:8–11.
27. Leyden JJ, Tanghetti EA, Miller B, et al. Once-daily tazarotene 0.1 % gel versus once-daily tretinoin 0.1 % microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis. 2002;69:12–9.
28. Webster GF, Berson D, Stein LF, et al. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. Cutis. 2001;67:4–9.
29. Cunliffe WJ, Danby FW, Dunlap F, et al. Randomised, controlled trial of the efficacy and safety of adapalene gel 0.1% and tretinoin cream 0.05% in patients with acne vulgaris. Eur J Dermatol: EJD. 2002;12:350–4.
30. Thiboutot D, Gold MH, Jarratt MT, et al. Randomized controlled trial of the tolerability, safety, and efficacy of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. Cutis. 2001;68:10–9.
31. Leyden J, Lowe N, Kakita L, Draelos Z. Comparison of treatment of acne vulgaris with alternate-day applications of tazarotene 0.1% gel and once-daily applications of adapalene 0.1% gel: a randomized trial. Cutis. 2001;67:10–6.
32. Thiboutot D, Arsonnaud S, Soto P. Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. J Drugs Dermatol. 2008;7:S3–S10.
33. Pariser D, Colon LE, Johnson LA, Gottschalk RW. Adapalene 0.1% gel compared to tazarotene 0.1% cream in the treatment of acne vulgaris. J Drugs Dermatol. 2008;7:S18–S23.
34. Shalita AMB, Menter A, Abramovits W, et al. Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. J Drugs Dermatol. 2004;4:153–8.
35. Webster GF, Guenther L, Poulin YP, et al. A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. Cutis. 2002;69:4–11.
36. Kunynetz RA. A review of systemic retinoid therapy for acne and related conditions. Skin Ther Lett. 2004;9:1–4.
37. Layton A. The use of isotretinoin in acne. Dermato-Endocrinol. 2009;1:162–9.
38. Agarwal US, Besarwal RK, Bhola K. Oral isotretinoin in different dose regimens for acne vulgaris: a randomized comparative trial. Indian J Dermatol Venereol Leprol. 2011;77:688–94.
39. Boyraz N, Mustak PK. Comparison of the efficacies of intermittent and continuous low-dose isotretinoin regimens in the treatment of moderate acne vulgaris. Int J Dermatol. 2013;52:1265–7.
40. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol. 2006;54:644–6.
41. Blasiak RC, Stamey CR, Burkhart CN, et al. High-dose isotretinoin treatment and the rate of retrial, relapse, and adverse effects in patients with acne vulgaris. JAMA Dermatol. 2013;149:1392–8.
42. Altinyazar HC, Koca R, Tekin NS, Esturk E. Adapalene vs. metronidazole gel for the treatment of rosacea. Int J Dermatol. 2005;44:252–5.

43. Chang AL, Alora-Palli M, Lima XT, et al. A randomized, double-blind, placebo-controlled, pilot study to assess the efficacy and safety of clindamycin 1.2% and tretinoin 0.025% combination gel for the treatment of acne rosacea over 12 weeks. J Drugs Dermatol. 2012;11:333–9.
44. Abokwidir MFS. Rosacea management. Skin Appendage Disord. 2016;2:26–34.
45. Park H, Del Rosso JQ. Use of oral isotretinoin in the management of rosacea. J Clin Aesth Dermatol. 2011;4:54–61.
46. Blok JL, van Hattem S, Jonkman MF, Horvath B. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. Br J Dermatol. 2013;168:243–52.
47. Jansen I, Altmeyer P, Piewig G. Acne inversa (alias hidradenitis suppurativa). J Eur Acad Dermatol Venereol. 2001;15:532–40.
48. Carretero GRM, Belinchón I, Carrascosa J, et al. Acitretina: guía de uso en psoriasis. Actas Dermo-Sifiliograficas. 2013;104:598–616.
49. Blair HA, Scott LJ. Alitretinoin: a review in severe chronic hand eczema. Drugs. 2016;76:1271–9.
50. Weinstein GD, Koo JY, Krueger GG, et al. Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. J Am Acad Dermatol. 2003;48:760–7.
51. Lebwohl M, Ast E, Callen JP, et al. Once-daily tazarotene gel versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. J Am Acad Dermatol. 1998;38:705–11.
52. Green L, Sadoff W. A clinical evaluation of tazarotene 0.1% gel, with and without a high-or mid-high-potency corticosteroid, in patients with stable plaque psoriasis. J Cutan Med Surg. 2002;6:95–102.
53. Behrens S, Grundmann-Kollmann M, Schiener R, et al. Combination phototherapy of psoriasis with narrow-band UVB irradiation and topical tazarotene gel. J Am Acad Dermatol. 2000;42:493–5.
54. Koo JY, Lowe NJ, Lew-Kaya DA, et al. Tazarotene plus UVB phototherapy in the treatment of psoriasis. J Am Acad Dermatol. 2000;43:821–8.
55. Kaur I, Dogra S, Jain R, Kumar B. Comparative study of calcipotriol (0.005%) ointment and tazarotene (0.05% and 0.1%) gel in the treatment of stable plaque psoriasis. Indian J Dermatol Venereol Leprol. 2008;74:471–4.
56. Mehta BH, Amladi ST. Evaluation of topical 0.1% tazarotene cream in the treatment of palmoplantar psoriasis: an observer-blinded randomized controlled study. Indian J Dermatol. 2011;56:40–3.
57. Sarkar R, Chugh S, Garg VK. Acitretin in dermatology. Indian J Dermatol Venereol Leprol. 2013;79:759–71.
58. Saurat JH, Geiger JM, Amblard P, et al. Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. Dermatologica. 1988;177:218–24.
59. Sommerburg C. Acitretin in combination with PUVA: a randomized double-blind placebo-controlled study in severe psoriasis. J Eur Acad Dermatol Venereol. 1993;2:308–17.
60. Tosti A, Ricotti C, Romanelli P, et al. Evaluation of the efficacy of acitretin therapy for nail psoriasis. Arch Dermatol. 2009;145:269–71.
61. Caldarola G, Zampetti A, De Simone C, et al. Circumscribed pityriasis rubra pilaris type IV. Clin Exp Dermatol. 2007;32:471–2.
62. Arnold AW, Buechner SA. Circumscribed juvenile pityriasis rubra pilaris. J Eur Acad Dermatol Venereol. 2004;18:705–7.
63. Dicken CH. Treatment of classic pityriasis rubra pilaris. J Am Acad Dermatol. 1994;31:997–9.
64. Petruzzi M, Lucchese A, Lajolo C, et al. Topical retinoids in oral lichen planus treatment: an overview. Dermatology (Basel). 2013;226:61–7.
65. Wolff M, Sabzevari N, Gropper C, Hoffman C. A case of lichen planus pigmentosus with facial dyspigmentation responsive to combination therapy with chemical peels and topical retinoids. J Clin Aesthet Dermatol. 2016;9:44–50.
66. Laurberg G, Geiger JM, Hjorth N, et al. Treatment of lichen planus with acitretin. A double-blind, placebo-controlled study in 65 patients. J Am Acad Dermatol. 1991;24:434–7.
67. Solak B, Kara RO, Kosem M. Palmoplantar lichen planus successfully treated with acitretin. BMJ Case Rep. 2015;2015:bcr2015211115.
68. Alsenaid A, Eder I, Ruzicka T, et al. Successful treatment of nail lichen planus with alitretinoin: report of 2 cases and review of the literature. Dermatology. 2014;229:293–6.
69. Kolios AG, Marques Maggio E, Gubler C, et al. Oral, esophageal and cutaneous lichen ruber planus controlled with alitretinoin: case report and review of the literature. Dermatology (Basel). 2013;226:302–10.
70. Kunz M, Urosevic-Maiwald M, Goldinger SM, et al. Efficacy and safety of oral alitretinoin in severe oral lichen planus–-results of a prospective pilot study. J Eur Acad Dermatol Venereol. 2016;30:293–8.
71. Digiovanna JJ, Mauro T, Milstone LM, et al. Systemic retinoids in the management of ichthyoses and related skin types. Dermatol Ther. 2013;26:26–38.
72. Fritsch P, Honigsmann H, Jaschke E. Epidermolytic hereditary palmoplantar keratoderma. Report of a family and treatment with an oral aromatic retinoid. Brit J Dermatol. 1978;99:561–8.
73. Cooper SM, Burge SM. Darier's disease: epidemiology, pathophysiology, and management. Am J Clin Dermatol. 2003;4:97–105.
74. Dogan S, Karaduman A, Erkin G, Gokoz O. Effective treatment of linear Darier's disease with topical retinoids: case report and review of the literature. Acta Dermatovenerol Croat. 2011;19:206–9.
75. Burge SM, Wilkinson JD, Miller AJ, Ryan TJ. The efficacy of an aromatic retinoid, Tigason (etretinate), in the treatment of Darier's disease. Br J Dermatol. 1981;104:675–9.
76. van Dooren-Greebe RJ, van de Kerkhof PC, Happle R. Acitretin monotherapy in Darier's disease. Br J Dermatol. 1989;121:375–9.
77. Dicken CH, Bauer EA, Hazen PG, et al. Isotretinoin treatment of Darier's disease. J Am Acad Dermatol. 1982;6:721–6.
78. Anuset D, Goutorbe C, Bernard P, Reguiai Z. Efficacy of oral alitretinoin for the treatment of Darier disease: a case report. J Am Acad Dermatol. 2014;71:e46–8.
79. Letule V, Herzinger T, Ruzicka T, Molin S. Treatment of Darier disease with oral alitretinoin. Clin Exp Dermatol. 2013;38:523–5.
80. Samuel M, Brooke RC, Hollis S, Griffiths CE. Interventions for photodamaged skin. Cochrane Database Syst Rev. 2005;CD001782.
81. Rabello-Fonseca RM, Azulay DR, Luiz RR, et al. Oral isotretinoin in photoaging: clinical and histopathological evidence

of efficacy of an off-label indication. J Eur Acad Dermatol Venereol. 2009;23:115–23.
82. Bagatin E, Guadanhim LR, Enokihara MM, et al. Low-dose oral isotretinoin versus topical retinoic acid for photoaging: a randomized, comparative study. Int J Dermatol. 2014;53:114–22.
83. Niles RM. Recent advances in the use of vitamin A (retinoids) in the prevention and treatment of cancer. Nutrition. 2000;16:1084–9.
84. Ianhez M, Fleury LF Jr, Miot HA, Bagatin E. Retinoids for prevention and treatment of actinic keratosis. Anais Brasil Dermatol. 2013;88:585–93.
85. Weinstock MA, Bingham SF, Digiovanna JJ, Veterans Affairs Topical Tretinoin Chemoprevention Trial G, et al. Tretinoin and the prevention of keratinocyte carcinoma (Basal and squamous cell carcinoma of the skin): a veterans affairs randomized chemoprevention trial. J Invest Dermatol. 2012;132:1583–90.
86. Lippman SM, Meyskens FL Jr. Treatment of advanced squamous cell carcinoma of the skin with isotretinoin. Ann Intern Med. 1987;107:499–502.
87. Nijsten TE, Stern RS. Oral retinoid use reduces cutaneous squamous cell carcinoma risk in patients with psoriasis treated with psoralen-UVA: a nested cohort study. J Am Acad Dermatol. 2003;49:644–50.
88. Anforth R, Blumetti TC, Clements A, et al. Systemic retinoids for the chemoprevention of cutaneous squamous cell carcinoma and verrucal keratosis in a cohort of patients on BRAF inhibitors. Br J Dermatol. 2013;169:1310–3.
89. Bianchi L, Orlandi A, Campione E, et al. Topical treatment of basal cell carcinoma with tazarotene: a clinicopathological study on a large series of cases. Br J Dermatol. 2004;151:148–56.
90. Peck GL, Gross EG, Butkus D, DiGiovanna JJ. Chemoprevention of basal cell carcinoma with isotretinoin. J Am Acad Dermatol. 1982;6:815–23.
91. Tangrea JA, Edwards BK, Taylor PR, et al. Long-term therapy with low-dose isotretinoin for prevention of basal cell carcinoma: a multicenter clinical trial. Isotretinoin-Basal Cell Carcinoma Study Group. J Natl Cancer Inst. 1992;84:328–32.
92. Carneiro RV, Sotto MN, Azevedo LS, et al. Acitretin and skin cancer in kidney transplanted patients. Clinical and histological evaluation and immunohistochemical analysis of lymphocytes, natural killer cells and Langerhans' cells in sun exposed and sun protected skin. Clin Transplant. 2005;19:115–21.
93. De Graaf YG, Euvrard S, Bouwes Bavinck JN. Systemic and topical retinoids in the management of skin cancer in organ transplant recipients. Dermatol Surg: Off Publication for Am Soc Dermatol Surg [Et Al]. 2004;30:656–61.
94. Heald P, Mehlmauer M, Martin AG, Worldwide Bexarotene Study G, et al. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol. 2003;49:801–15.
95. Abbott RA, Whittaker SJ, Morris SL, et al. Bexarotene therapy for mycosis fungoides and Sézary syndrome. Br J Dermatol. 2009;160:1299–307.
96. Querfeld C, Rosen ST, Guitart J, et al. Comparison of selective retinoic acid receptor- and retinoic X receptor-mediated efficacy, tolerance, and survival in cutaneous t-cell lymphoma. J Am Acad Dermatol. 2004;51:25–32.
97. Hamnvik OP, Larsen PR, Marqusee E. Thyroid dysfunction from antineoplastic agents. J Natl Cancer Inst. 2011;103:1572–87.
98. Scarisbrick JJ, Morris S, Azurdia R, et al. U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. Br J Dermatol. 2013;168:192–200.
99. Tousi B. The emerging role of bexarotene in the treatment of Alzheimer's disease: current evidence. Neuropsychiatr Dis Treat. 2015;11:311–5.
100. Walmsley S, Northfelt DW, Melosky B, et al. Treatment of AIDS-related cutaneous Kaposi's sarcoma with topical alitretinoin (9-*cis*-retinoic acid) gel. Panretin Gel North American Study Group. J Acquir Immune Defic Syndr. 1999;22:235–46.
101. Spielvogel RL, DeVillez RL, Roberts LC. Oral isotretinoin therapy for familial Muir–Torre syndrome. J Am Acad Dermatol. 1985;12:475–80.
102. Marcusson JA, Bjarnason B, Ros AM. Isotretinoin for sebaceous skin lesions in Muir-Torre syndrome: a case report. Acta Derm Venereol. 1998;78:479–80.
103. Graefe T, Wollina U, Schulz H, Burgdorf W. Muir–Torre syndrome – treatment with isotretinoin and interferon alpha-2a can prevent tumour development. Dermatology. 2000;200:331–3.