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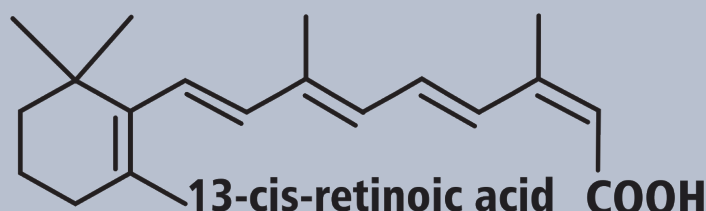
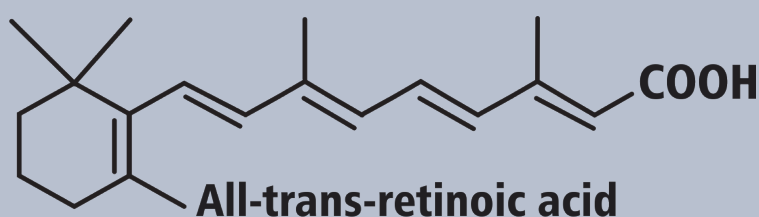
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„OFF-LABEL USES OF RETINOIDS IN DERMATOLOGY”

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OFF-LABEL USES OF RETINOIDS IN DERMATOLOGY

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Abstract

Retinoids has been used widely in the topical and systemic treatments of various dermatoses: psoriasis, disorders of keratinization (DOK), keratotic genodermatosis, and severe acne. Moreover, it is also used in the treatment and/or chemoprevention of skin cancer and other neoplasms. Retinoids display key regulatory functions and most dermatologists are familiar with the FDA-approved indication of this medication. Retinoic acid is a potent signaling molecule that is essential for many biological processes, and its levels are tightly regulated by mechanisms that are only partially understood. This article will review these recent findings and attempt to synthesize their meaning to provide a view into the off-label uses of retinoids in dermatology with an emphasis on oral isotretinoin and acitretin.

Key words: off-label uses; dermatoses; isotretinoin; acitretin; systemic and topical use

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Introduction

Now retinoids have been applied in treating various dermatoses and in this study, we will review its recent „off-label” uses, referring to those usages which haven't been shown in the indications but have been proved to be effective and beneficial in clinical practice for years.” after „It is the first retinoid or arotinoid that selectively acts through the retinoid X receptors (RXRs) and is mainly used in Cutaneous T-cell lymphoma (CTCL) [1-3].

It's well known that three generations of retinoids have been established for systemic and topical treatment of various skin disorders (Tabl. I). The first generation includes the nonaromatic retinoids β -carotene (provitamin A), all-trans-retinoic acid (RA, tretinoin), and 13-cis-RA (isotretinoin). The second generation is the monoaromatic retinoids etretinate and acitretin and the third is the polyaromatic retinoid derivatives tazarotenic acid and adapalene [1]. The first retinoid 13-cis-retinoic acid (also known as isotretinoin) was synthesized in 1955. However, only until 1973 was it first used to treat psoriasis in Europe. Three years later, it was approved in the United States for treating severe nodulocystic acne that has not responded to standard therapy. Since 1982, it has been marketed by Hoffmann-La Roche under the trade name Accutane. The aromatic retinoid etretinate was synthesized in 1972 and has also received extensive attention. However, etretinate has been replaced by acitretin because of its long half-

life. Bexarotene represents the third novel generation of vitamin A analogs. It is the first retinoid or arotinoid that selectively acts through the retinoid X receptors (RXRs) and is mainly used in Cutaneous T-cell lymphoma (CTCL) [1-3].

Pathways for Retinoid Therapies in Dermatology

1. Effects on cell proliferation

a. Retinoids inhibit ornithine decarboxylase activity in response to by a variety of hyperproliferative stimuli. They inhibit cell growth dose dependently and potentiates epidermal growth factor (EGF) and heparin-binding-EGF induced cell proliferation [4,5].

b. Retinoids increases the level and activity of AMP-dependent protein kinases which are deficient in human psoriatic fibroblasts, leading to increased growth-inhibitory effect of cAMP in fibroblast [6,7].

2. Anti-inflammatory effect

a. Retinoids reduce the release of leucotrienes and dihydroeicosatetraenoic acid products and inhibits neutrophil chemotaxis. In T cells, RA blocks the inhibitory effects of inflammatory cytokines, such as IL-6, on the TGF β mediated Foxp3 induction via the activation of RAR receptors (Ref). RA improves clinical symptoms and reduces the levels of inflammatory cytokines, including IL-6, TNF- α and IFN γ [8,9].

Systemic retinoids		
Substance (major registrations)	Recommended dose	Major indications
Acitretin	0.5 mg/kg/day p.o.	Chronic plaque psoriasis
	1.0 mg/kg/day p.o.	Pustular psoriasispsoriasis
	0.25 mg/kg/day p.o.	Erythrodermic psoriasis
	0.5 -1mg/kg/day p.o.	DOK (e.x Lamellar ichthyosis, Darier disease)
Bexarotene	300 mg/m ² /day p.o.	Cutaneous T-cell lymphoma
Isotretinoin	0.5–1 mg/kg/day p.o.	Severe acne and acne-related dermatoses
Tretinoin	45 mg/m ² /day p.o.	Acute promyelocytic leukaemia

Table I. Approved retinoids and indications

However, RA decreases the expression of inflammatory markers in psoriasis, including HLA-DR, ICAM-1 and IL-6 [10].

b. RA interferes with the esterification and incorporation of arachidonic acid into nonphosphorus lipids in human keratinocytes and hence reduces inflammation in psoriatic plaques [11,12].

c. RA inhibits ornithine decarboxylase, the rate-limiting enzyme for synthesizing polyamines, thus lessening the inflammatory hyperplasia [13].

3. Anti-neoplastic and anti-tumor effects

The mechanism for the anti-neoplastic and anti-tumor effects of RA is currently unclear. Acitretin inhibits the invasiveness and metastatic potential of the adenocarcinoma cells. Retinoids modulate cell growth and differentiation in a variety of human tumors. They are particularly effective in T-cells and Hodgkin lymphoma cell lines and inhibit cell growth by arresting cells in the G1-phase or induce apoptosis. They reduce the expression of antiapoptotic bcl-2 protein and upregulate proapoptotic bax-proteins [14,15].

4. Effects on embryogenesis and morphogenesis

Retinoids participate in the formation of diverse embryonic structures (face, heart, eye, limb and nervous system) [16,17].

5. Effects on intercellular matrix components

At physiologic concentrations, RA increases mucopolysaccharides, collagen and fibronectin synthesis and decreases collagenase production. At nonphysiologic concentrations, RA inhibits the proliferation of human fibroblasts and synthesis of collagen type III and I and affects wound healing [18-21].

6. Anti-pigmentation

Clinical studies have shown that topical RA treatment improves the irregular hyperpigmentation associated with previous UVR exposure, melasma and inflammation. Lightening of actinic lentigines and mottled hyperpigmentation correlates with a reduction in epidermal melanin content; this is possibly resulted from inhibition of tyrosinase activity and reduction of melanin content transport to keratinocyte. RA appears to activate resting melanocytes and augments UVR stimulation of melanogenesis; however, they do not alter or reduce melanogenic activity in pigment cell. RA may not augment UVR-induced melanin production;

in instead, they increase the number of active melanocyte, resulting in reduced melanogenesis [22-25].

7. Anti-sebum effects

The first generation retinoids and acitretin inhibit sebocyte proliferation in a dose and time dependent manner. Isotretinoin is the most potent inhibitor of lipid synthesis. 13-cis-RA was given systemically in severe forms of acne. It is the only retinoid that can markedly diminish sebostatic activity [26,27].

8. Effects on immunomodulation

RA increases in the percentage of peripheral blood lymphoid cells expressing surface markers for T-helper cells with only minimal effect on natural killer cell marker expression. RA upregulates antigen presentation by Langerhans cell and stimulates the expression of surface marker HLA-DR and CD11c that is a b-2 integrin critical for T-cell activation. Retinoids also enhance IFN- γ production, which is partially mediated by IL-12 induction and is synergized by IL-2. This results in upregulation of major histocompatibility complex and a shift from T-helper 2 cells to T-helper 1 cells. In addition, RA enhances the cytotoxic activity of natural killer cells and mimics some biologic effects of IFN [28,29].

9. Other function

The architecture of epidermis obtained in vitro by growing adult human keratinocytes on a dermal substrate can be modulated by retinoids.

Receptors for the Pleiotropic Functions of Retinoids

The pleiotropic effects of retinoids are mediated through two families of nuclear retinoid receptors, retinoic acid receptors (RAR α , - β and - γ) and retinoid X receptors (RXR α , - β and - γ). RARs and RXRs are modular proteins containing domains responsible for sequence-specific DNA binding (C-region), ligand independent trans-activation (AF-1, A/B region), and ligand-dependent trans-activation (AF-2, E-region) [30]. In skin cells, the predominant retinoid receptor is the RAR- γ /RXR- α heterodimer [31]. The endogenous ligands for RARs are all-trans retinoic acid (ATRA) and 9-cis retinoic acid (9-cis RA) and the endogenous ligand for RXRs is 9-cis RA [30,31]. Depending on their chemical structure, retinoids differ in their interaction with the cellular receptors.

Depending on their action, panagonists that bind to both receptors can be distinguished from selective RAR or RXR agonists. Retinoids exert some of their effects by binding to RAR or RXR in the nuclei of cells for binding to DNA and interact with other transcription factors. RAR and RXR consist of three isoforms (i.e., α , β , and γ) that forms heterodimers to bind to particular DNA sequences called "retinoic acid response element". Thereby, these receptors act as transcription factors either directly or indirectly to regulate the expression of retinoid-responsive genes. Dysfunction of these nuclear receptor signaling could lead to proliferative and reproductive and metabolic disease [32] and Acne isoform Dermatosis.

Side Effects of Retinoids

Retinoids have significant adverse effects like teratogenic potential, hyperlipidemia, mucocutaneous, diffuse idiopathic hyperostosis, liver toxicity, and pseudotumor cerebri-like symptoms. Women of childbearing age should use adequate contraception for at least three years after discontinuing the use of acitretin. Isotretinoin is an option in women of childbearing age as its elimination half life is short and adequate contraception should be maintained for at least one month after stopping the drug [33-36]. Patients may experience generalized pruritus [34,36,37]. The most common side-effects of systemic isotretinoin administration are dry mucous membranes, nose bleed, and dry skin. Eye dryness is related to the dose used, at least during the period of treatment. Conversely, the rate of conjunctival *S aureus* colonization was unrelated to the dose of isotretinoin [38]. In fact, some degree of cheilitis is an indication for sufficient bioavailability and to some extent, can be a parameter to individualize the optimal dosage [39-42]. However, a more serious side effect is the development of skeletal hyperostosis, in which new bone forms in areas of ligamentous attachment. This occurs in long-term high-dose treatment with isotretinoin. It is currently recommended that skeletal radiologic surveys be carried out at the start and after six and twelve months of treatment in patients receiving high doses of isotretinoin [43,44]. In the central nervous system the side effects of retinoids are rare and range from mild headache to visual changes and papilledema [45]. The syndrome of pseudotumour cerebri has been reported in a small number of patients receiving isotretinoin; some of them were also taking either tetracycline or minocycline [46]. It is not known whether this represents a drug interaction; however, it seems prudent to avoid using these antibiotics concurrently with isotretinoin [47,48]. Most recently, the occurrence of hyperuricemia has been reported in patients receiving isotretinoin [49]. The efficacy of systemic retinoid therapy in a number of dermatologic diseases is well established, however, concerns about potential side effects limit their use, especially in children. So contraindicated in neonates unless the condition is life threatening (harlequin fetus) [50,51]. Prolonged therapy requires monitoring of bone structures and should be used in exceptional circumstances. Furthermore, the incidence of adverse events appears to be higher in old people. Overall, it is recommended that clinic use of retinoids requires frequent monitoring (Tabl. II) [52-

26]. Patients should be maintained on the lowest effective retinoids dose for minimizing the occurrence of these side effect.

Serum triglyceride level occurs commonly with isotretinoin therapy, usually ranging between 2.25 and 4.50 mmol/L. Over the first four weeks of treatment the concentrations of low- and very-low density lipoproteins and cholesterol increase and the level of high-density lipoprotein decreases. The levels then stabilize and return to normal within 8 weeks after treatment is stopped. Therapy should be stopped if the triglyceride level exceeds 8.0 mmol/L because of a risk of pancreatitis [37,57]. More dramatic increases in the triglyceride level have been observed in patients who were obese, consumed excessive amounts of alcohol, had a family history of hyperlipidemia or other risk factors [58]. Patients at risk should be put on a low-fat diet and have their alcohol intake limited in an attempt to prevent the triglyceride level from increasing [59,60]. The retinoids are not stored in the liver, but they are metabolized there; thus the liver is a potential site of toxic effects. The mildly abnormal results of liver function tests sometimes are often corrected while treatment continues and are reversible once it is stopped. Other abnormalities that seem to have had no clinical significance include increases in the peripheral blood platelet count and total protein level and in the urine specific gravity and leukocyte count [50]. Currently, clinical monitoring requires physic examination and laboratory parameters every 4 weeks to manage mucocutaneous or organ adverse effects and ensure compliance.

Off-label Uses of Retinoid in Dermatology

I. Keratinization diseases

Acitretin has achieved a widespread clinical use in the treatment of severe psoriasis and other keratinization diseases. It has a terminal elimination half-life of about 55 to 60 hours. However, concomitant intake of alcohol induces its transformation to etretinate that has a longer terminal elimination half-life (84 to 168 days) [60,61]. Acitretin is effective in cutaneous disorders of keratinization (ichthyosis, palmo-plantar keratoderma, Darier's disease) [62,63]. When taken orally, isotretinoin is rapidly absorbed, with peak levels being reached in 2 to 3 hours. Virtually all of the drug is bound to albumin and is metabolized to 4-oxo-isotretinoin. The elimination half-lives with either single or multiple dosing are 10 to 20 hours and 24 to 29 hours for the drug and its metabolite respectively. Systemic isotretinoin has been used to treat severe acne vulgaris for more than 20 years [41,64]. However, isotretinoin also represents a potentially useful choice of drugs in many dermatologic diseases other than acne vulgaris. Diseases such as psoriasis, pityriasis rubra pilaris, condylomata acuminata, skin cancers, rosacea, hidradenitis suppurativa, granuloma annulare, lupus erythematosus and lichen planus have been shown to respond to the immunomodulatory, anti-inflammatory and antitumor activities of the drug. Isotretinoin also helps prevent skin cancers such as basal cell carcinoma or squamous cell carcinoma [64-66].

Systemic retinoids	
Symptom / Complaint	Treatment
Mucocutaneous system	Occur in nearly all patients receiving Isotretinoin and acitretin, but rarely lead to drug
Cheilitis, dryness of the eyes, nasal and oral mucosa [36-39]	Topical lubricants, application of artificial tears and nose drops
Epistaxis [37]	Topical lubricants
Dry skin, skin peeling [34-36]	Topical lubricants
Palmoplantar desquamation	Topical lubricants
Pruritus [34,36,37]	Topical lubricants, and by avoiding exposure to sunlight Antihistamine drug (no improvement to another treatment)
Temporary aggravation of the diseases	During the first 4 weeks
Acne may temporarily become worse [39,40]	Oral administration of corticosteroids
Aggravation of psoriasis with an increase of the body surface area involved [41]	Topical retinoids or combined with a topical corticosteroid
Retinoid dermatitis	Mimic unstable psoriasis
Excessive granulation tissue [42,43]	At the site of healing cystic acne and adjacent to nail plates in patients treated with isotretinoin and etretinate respectively, laser and dermabrasion can improve symptom
Mental symptoms [52]	No need treatment
Hair texture, hair and eyebrows loss and thinning of the hair [53-55]	No special treatment reported
Brittle nails [37]	No special treatment reported
Abnormal menstruation [56]	Reduced the daily dose and discontinued retinoids
Sore throat	Should be referred for appropriate care
Urticaria	Antihistamine drug
Diarrhoea	Antidiarrheal, if necessary, relieve the drug dose
Headache, visual changes, nausea, vomiting	Examination for papilledema and discontinued the retinoids
Lower back pain	Giving analgesic if can't endure the pain
Yellow discoloration of skin	Not documented

Table II. The side effects of systemic retinoids

We have gathered most of the “unapproved” conditions treated with isotretinoin and/or acitretin no attempt of classifying the publications at the level of “evidence based” partly only clinic reports. In fact, many other diseases have been treated, which overlap the list of diseases treated with isotretinoin or acitretin. The choice of acitretin rather than isotretinoin was not based on pharmacological considerations. Many skin disorders respond to acitretin, but the effect of use of isotretinoin treating the same diseases is established in controlled studies for only a few of them. Thus, the choice still depended on sex, age, the reaction of patients to drugs, and side effects.

Psoriasis and other Keratinization disorders

35 to 40 mg daily is the average effective dosage of acitretin given daily in adults, while 0.5 mg/kg/day is effective in children. It promotes keratinocyte differentiation to clear keratinization disorders, including severe psoriasis,

congenital ichthyoses (autosomal dominant ichthyosis vulgaris, follicular ichthyosis, Bullous ichthyosiform erythroderma), Darier's disease and pityriasis rubra pilaris and palmoplantar keratoderma, erythrokeratoderma variabilis, symmetrical progressive erythrokeratoderma Kyrle-Flegel, pityriasis rotunda, Verrucous epidermal naevus, Vohwinkel's syndrome [63,67-69]. Isotretinoin appears partially inferior to acitretin in the skin diseases. Except for strong sebostatic action, it has a much shorter half-life than acitretin. Isotretinoin is an alternative to acitretin-PUVA in fertile women in whom prolonged contraceptive restriction is unacceptable or associated with a risk of noncompliance. Some dermatologists continue to use isotretinoin in female patients with psoriasis who need systemic retinoids in order to avoid the long-term teratogenic effect of acitretin. The average effective dose of isotretinoin was 2 mg/kg/day in adults [65,70]. The excellent outcome appeared in a 16-year-old girl with pustular psoriasis with isotretinoin [71].

A multicenter study of the effectiveness of isotretinoin in lamellar ichthyosis and epidermolytic hyperkeratosis was conducted. Almost all of the patients in both groups were clearly improved, and the degree of improvement seemed higher in the group of patients with lamellar ichthyosis. The average effective dose of isotretinoin was 2 mg/kg/day. Patients found it to be more helpful and acceptable than any previous treatment they had been given. Patients with the most severe disease cleared less completely. Very gratifying responses noted by the lamellar ichthyosis patients were the ability to sweat, with increased heat tolerance and improvement in ectropion [72].

Porokeratosis

A 73-year-old woman with porokeratosis was initially treated with isotretinoin 60 to 80 mg daily, which resulted in a decrease in the number of lesions on the body and in the hyperkeratosis of the papules on the palms and soles. In 1985, the medication was changed to etretinate in doses that ranged from 25 to 50 mg, which resulted in even more effective results in decreasing the number of lesions and the palmoplantar hyperkeratosis. In 1998, after etretinate was removed from the market, acitretin was initiated at a dose of 25 mg daily, with similar clinical efficacy as the parent compound. Porokeratosis was found in younger women without any significant past medical history. Oral isotretinoin showed moderate improvement [73-75].

Chronic Hand Dermatitis (CHD)

Topical treatment with bexarotene gel for 22 weeks has been investigated in an open label randomized (into 3 treatment arms) study including 55 patients with CHD. According to the physician assessment (PA) bexarotene gel (BG) was comparative in effects to bexarotene gel combined with topical mometasone furoate (MF) ointment 0.1% (BG+MF) and superior to BG in combination with topical hydrocortisone ointment 1% (BG+HC). An improvement of over 50% was seen in 79% of the BG arm, 77% in the BG +MF arm and 50% of the BG+HC arm. In a single-blinded randomized study treatment of hyperkeratotic hand eczema with 30 mg of acitretin daily or placebo, acitretin was found to be statistically significantly more effective than placebo. There was an overall 51% reduction in clinical symptoms after 4 weeks in the acitretin group compared with a 9% reduction in the placebo group. In 1999 alitretinoin was described as an effective treatment for CHD after an open-label study with oral 9-cis-retinoic acid. It included 38 patients with the following diagnoses: pompholyx, hyperkeratotic eczema, fingertip eczema and discoid eczema, all with unsatisfactory response to previous treatments. All patients were given a once daily oral dose of 20 or 40 mg alitretinoin, in a mean duration of 2.3 months (range 1–5 months). In that study 89% showed a very good or good therapeutic response (TR), 5.5% a moderate TR and 5.5% had no response [76,77].

Atrophoderma vermiculatum

A 2-year-old girl was treated with isotretinoin with successful induction of remission in the inflammatory component

of the disease following a prolonged course of therapy. Improvement was then maintained after cessation of the treatment. Isotretinoin may lead to long-term suppression of lesions. Such treatment needs to be given in the active or inflammatory stage for best results and to be continued for a sufficient duration to give a good clinical response [78].

Ulerythema ophryogenes

A woman with an unresponsive disease to multiple topical and systemic therapies was treated with oral isotretinoin with no definitive but prolonged periods of improvement [79].

Papillon-Lefevre syndrome

Two children were treated with acitretin 0.5 mg/kg of body weight per day from November 1992 to November 1993, and another child since October 1993. Concurrently, the children received professional oral hygiene care (scaling, root planing, and curettage). The combination of retinoid therapy and periodontal treatment improved the dermatologic and periodontal conditions. Two female patients were treated with oral isotretinoin with remarkable improvement of the keratoderma, the fissures, and the pain. Treatment was not curative, and discontinued therapy caused the recurrence of the keratoderma [80-82].

Erythrokeratodesmia variabilis

A woman who was treated with isotretinoin showed almost complete clinical clearing of the hyperkeratotic plaques, and her palmo-plantar keratoderma improved as well. Migratory erythematous patches cleared quickly but did recur occasionally in an unpredictable manner. However, hyperkeratotic plaques and migratory erythematous patches reappeared within 2 weeks of discontinuation of the therapy. A restoration of normal numbers of epidermal keratinosomes within hyperkeratotic plaques was observed by electron microscopy [83,84]. A patient with erythrokeratoderma variabilis is presented and responded to acitretin. An initial dose of 35 mg of acitretin and a maintenance dose of 25-35 mg resulted in pronounced and sustained improvement. At the histological level the extensive hyperkeratosis and the moderate dermal inflammatory infiltrate decreased during treatment with acitretin. In comparison with the other retinoids available to date, acitretin is the derivative of the first choice in the treatment of erythrokeratoderma variabilis [85].

II. Adnexal Diseases

Acne and Related Conditions

Oral isotretinoin is unique among acne treatments because it exhibits activity against all major etiologic factors involved in the pathogenesis of acne. Since introduced in 1982, oral isotretinoin has revolutionized acne therapy and still is the „Gold standard” in the treatment of acne and its variants. The recommended dose to start isotretinoin therapy is 0.5mg/kg [86]. In some cases, acitretin is an effective alternative to isotretinoin for acne treatment.

For example, there is a 14-year-old boy whose facial acne was resistant to oral antibiotic treatment. After treated with 0.3mg/kg acitretin (Neotigason) daily for 5 months the patient has an excellent response. Hidradenitis suppurativa (HS) is a distressing chronic inflammatory skin disorder which affects predominantly the groins and axillae. In analogy to acne, oral isotretinoin has been considered for treating HS, although there are strong indications that this drug has only a very limited therapeutic effect. During the past 25 years scattered case reports have described promising results of treatment with acitretin. Acitretin appears to be an effective treatment for refractory HS, leading to reduction of pain from painful nodules and reducing the extent of the disease for a prolonged period [87]. Scheman reported a case of a patient with severe nodulocystic facial acne and hidradenitis suppurativa that was treated with 2 full courses of isotretinoin in 2002. Although the patient's condition improved, some draining cysts persisted on the face and groin. Because of the inability of isotretinoin to achieve long-term remission of the patient's condition, acitretin was considered as a possible maintenance drug. The patient was almost completely improved after 5 months' therapy with acitretin, which also was effectively used for ongoing maintenance. Acitretin may be a promising treatment for severe nodulocystic acne and hidradenitis suppurativa, which require long-term suppression when isotretinoin fails to give long-term remission [88]. A 10-month-old patient with comedones resistant to multiple antibiotic regimens was treated with isotretinoin (5 to 10 mg/day) for 5 months with excellent results. Oral isotretinoin may be safe and effective in cases of recalcitrant infantile acne; however, it should be used with caution if longer periods are necessary because of the well-known side effects of oral retinoids [89].

Rosacea

In severe forms or treatment-resistant rosacea, isotretinoin may be more effective on inflammatory lesions than on erythema and telangiectasia with a long-lasting favorable effect. Histopathologically, isotretinoin has been shown to reduce lymphohistiocytic perivascular infiltration, edema, and the number of ectatic vessels in patients with rosacea. Isotretinoin 0.3 mg/kg is an effective and well-tolerated therapy option for the treatment of rosacea subtype II and III and can therefore be used successfully as an alternative to therapy with oral antibiotics [90].

Solid facial edema

Isotretinoin alone is beneficial in some cases; however, combined therapy with isotretinoin and ketotifen or clofazimine results in better clinical outcomes. The therapeutic combination of oral isotretinoin (0.5 mg/kg body weight daily) and ketotifen (2 mg daily) led to complete resolution of all facial lesions [91].

Steatocystoma multiplex

A small number of patients with this condition have been treated with isotretinoin with variable responses. Frequently, the abscesses involuted and inflamed cysts markedly improved; however, remission persisted only a few weeks

after discontinuation of the therapy. In one case, patient discontinued therapy before a response occurred and then showed a response later. Apaydin treated a 30-year-old patient of steatocystoma multiplex with oral isotretinoin (1 mg/kg per daily) for 6 months. At the same time, cryotherapy was used for non-suppurating lesions smaller than 2 cm. When the patient was evaluated 6 months later, cosmetic results were good. No new lesions have appeared in the subsequent 12-month follow up [92].

Sebaceous hyperplasia

Oral isotretinoin was given to three patients who showed marked improvement in skin texture; reduction in the size of the lesions and facial seborrhea occurred after 6 weeks. Long-term therapy with a lower dose of isotretinoin was given to maintain this improvement. The authors reported the case of a 57-year-old Caucasian female with a longstanding history of sebaceous hyperplasia refractory to treatment on her face. Isotretinoin was used as an alternative therapy and was found to be effective [93].

Fox-Fordyce disease

Fox-Fordyce disease (apocrine miliaria) is predominantly observed in women. A male patient with typical features of this disorder is described. Oral treatment with isotretinoin resulted in temporary relief [94].

Pyoderma faciale

The explosive onset of fluctuant facial papulonodules, usually in young women, is characteristic of pyoderma faciale. This disorder is neither a true pyoderma nor a variant of acne, but rather a severe form of rosacea. The most effective therapeutic modality appears to be isotretinoin, especially if preceded by a brief course of oral corticosteroids or a short interval of application of potent topical corticosteroids. Despite the concern about the potential adverse effects of systemic retinoids on underlying inflammatory bowel disease, isotretinoin was given to a patient with refractory pyoderma faciale. Response was dramatic, and no ill effects were encountered [95].

Eosinophilic pustular folliculitis (Ofuji's disease)

The efficacy of isotretinoin may involve the inhibition of the eosinophilic chemotactic factors, presumptively present in the sebaceous lipids and the stratum corneum of patients suffering from eosinophilic pustular folliculitis. Berbis (1989) reported a case of a 30-year-old man with a 6-year history of eosinophilic pustular folliculitis (EPF). Isotretinoin (1 mg/kg/day) led to a dramatic improvement of all the lesions within 2 weeks. However, a recurrence of the papulopustular, follicular and pruritic lesions after was followed by 10 days after drug withdrawal. The mechanisms underlying this efficacy may involve the inhibition of the eosinophilic chemotactic factors thought to be present in sebaceous lipids and in the stratum corneum of patients suffering from EPF. Acitretin (0.5 mg/kg/d) was then started and led to cure within 1 month.

Six weeks after the patient spontaneously stopped the treatment, the lesion recurred at the same localization. Further treatment with isotretinoin (0.5 mg/kg/d) was then given but did not alter the progression of the lesion. Acitretin was then reintroduced at the same dose and again produced rapid cure. Acitretin was then tapered off to 10 mg/d then maintained at this dose as lesions reappeared with further dose reduction. Isotretinoin is proposed on the hypothesis of a link with sebaceous secretion, but results have been contradictory [96,97].

Actinic folliculitis

Oral isotretinoin was highly effective in two female patients who did not obtain clinical improvement with standard treatments. The treatment was administered for 3 and 6 months, respectively, with persisting clinical resolution [98].

AIDS-associated eosinophilic folliculitis

Seven patients were treated with oral isotretinoin, with rapid clinical and symptomatologic remission. Four of seven patients experienced lasting remission from one course of therapy, while three others suffered brief relapses, necessitating one to three further courses of isotretinoin therapy. Side effects were tolerable, and no apparent adverse effects on patients' immune status were noted [99].

Multiple syringomas

Two female patients were treated for 5 to 6 months with isotretinoin. After therapy, the lesions were flattened, softened, and skin colored in both patients. Histologically, a marked reduction in the size and numbers of syringomas was observed, and the contents of cystic lesions seemed reduced 6 months following therapy. Ultrastructurally, changes in the cystic and ductal epithelium correspond to the keratin-modulating efficacy of the drug, but a drug-induced change in intracellular lipid composition was also observed [100].

III. Cancers and Precancerous Conditions

A number of experimental and clinical studies performed in the past two decades show that with retinoids inhibit or reverse the carcinogenic process in some organs. Possible mechanisms by which retinoids may hinder the development of skin cancer include inhibition of tumour initiation and promotion, induction of normal cell differentiation and immunomodulation.

BCC and SCC

Cutaneous basal-cell or squamous-cell carcinomas were treated with isotretinoin orally at a dose of 2 mg/kg/day for 2 years and then followed by 1 year after stopping the drug. The rapid onset of isotretinoin's chemopreventive efficacy, as well as its rapid loss, suggests that the drug is acting late in the course of events that lead to malignancy. Combined therapy with isotretinoin and INF-2 α was highly effective in advanced squamous cell carcinoma. Acitretin treatment (30-50 mg/day over 6 months) appears to decrease the number

of new squamous cell carcinomas and ameliorates the aspect and reduces the number of actinic keratoses [101-103].

Bowen disease

Patients of old age with multiple lesions of Bowen diseases could not accept surgical treatment. The choice of a chemotherapy combining oral isotretinoin with subcutaneous IFN α is more effective. The patient responded well to the treatment. The small lesions resolve after 1 month of therapy, and the largest lesions improved significantly but did not disappear completely. Although the treatment of choice for Bowen disease is surgical excision, an attempt of medical therapy could prevent significant surgical morbidity [104].

Cutaneous t-cell lymphoma (CTCL)

Three traditional retinoids, isotretinoin, etretinate, and acitretin, acting through RAR, are the first retinoids tested for activity in CTCL. Therapies combining retinoids with psoralen-ultraviolet A or with IFNs may have a synergistic effect, which deserves confirmation through randomized trials in the future. Among patients with CTCL in the current study, the response rate to the combination of IFN- α and isotretinoin is 33%. The combination induces higher levels of IFN-stimulated genes than either agent alone. Isotretinoin is effective in both early and advanced stages of mycosis fungoides as an initial treatment to induce a rapid remission. To sustain or even improve the beneficial effect, isotretinoin may be combined with other therapeutic modalities. Se'zary syndrome apparently does not respond to retinoid treatment. Isotretinoin (1 to 2 mg/kg/day) and acitretin (initial dosage of 25 mg/day during the first week, and was increased to 50 mg/day from weeks 2 to 48) were considered to be of equal potency in the treatment of mycosis fungoides [105]. However, it is impossible to maintain the remission with retinoids monotherapy; usually, these responses are of short duration and relapses are common. Combined treatment with recombinant IFN α and isotretinoin has been used in patients with mycosis fungoides, followed by total skin electron beam therapy alone (for stage I to II disease) or preceded by chemotherapy (for stage III to IV disease) [106-108]. The new generation of retinoids, the RXR selective agonists like bexarotene has been approved by the FDA for the treatment of all stages of CTCL in patients refractory to at least one systemic therapy. The drug is effective for the treatment of all stages of CTCL, as both an oral capsule and a topical gel formulation in 2000. The RXR-selective retinoid, bexarotene, induces apoptosis in CTCL cell lines in vitro without inhibiting DNA or inducing differentiation that is associated more with RAR agonists [108,109].

Metastatic melanoma

Twenty-five patients were treated with isotretinoin orally (1 mg/kg/day) and recombinant IFN α -2a subcutaneously at 3 million units daily for 16 to 48 weeks. Two patients achieved a complete response, and three responded partially for a total response rate of 20%. Responses occurred primarily in patients with limited tumor burden and disease confined to the skin and lymph nodes.

Significant elevations in peripheral blood 29-59-oligoadenylate synthetase activity and NK cell activity were observed with therapy. The effect of 13-cis-retinoic acid and highly purified human leukocyte IFN α (Alphaferon) therapy for metastatic melanoma was studied [110]. A group of 17 patients with disseminated malignant melanoma were treated over a 6-month period. They received 60 mg 13-cis-retinoic acid daily continuously and ten cycles of IFN α . IFN was administered by subcutaneous injection, at a daily dose of 6×10^6 IU. The 5-day treatment period was followed by an IFN-free interval of 2 weeks. An overall response rate of 30% with 12% complete responses (2 out of 17 patients) was reported [111].

Malignant eccrine poroma

A patient was treated with isotretinoin that induced a partial remission lasting for 8 weeks with minimal toxicity. The mechanism of action is unknown; however, local tumor necrosis with sparing of the adjacent normal tissue is highly suspicious [112].

Malignant metastatic eccrine poroma

A new chemotherapy protocol consisting of isotretinoin and has confirmed the advantages of polychemotherapy in one case of malignant eccrine poroma with metastatic regional lymph nodes. With this chemotherapy, arrest of the metastatic progression was achieved after 3 months, and the remission was maintained until the 10th month of therapy [113].

Langerhan cell histiocytosis

A male patient was treated with oral isotretinoin. Complete remission of the single-system skin disease of the patient was observed after an 8-month therapy. The patient completed a 5-year follow-up and remained free of recurrence and of visceral involvement [114]. A 57-year-old man presented with a 2-year history of bilateral erosive lesions on the inguinal region, and erythematous, brown and crusted papules over the trunk. The patient was treated with oral acitretin for 1 year (with a topical corticosteroid for the inguinal lesions), resulting in clearing of the cutaneous lesions. He underwent placement of bilateral double-J ureteral catheters and was started on hormone replacement therapy. At follow-up 1 year after treatment with acitretin ceased, the patient remained free of cutaneous lesions and his overall condition, including the retroperitoneal fibrosis, had improved. This case had an uncommon combination of features, with a good response to acitretin [115].

Skin cancer in renal transplant patients

Renal transplant recipients have an increased risk of developing skin cancers, which are often multiple and aggressive. Frequently, these tumors develop on a background of widespread epidermal dysplasia. Systemic retinoids are known inhibitors of skin cancer but reports of their use in renal transplant patients are limited. Transplant patients with multiple cutaneous squamous cell carcinomas may greatly benefit from low-dose isotretinoin administration (0.2 to 0.5

mg/kg/day) to prevent the development of new skin cancers and slow the progression of existing neoplasms. There has been no adverse effect on the transplanted kidney and no changes in patient's immune status. Well tolerated low-dose acitretin (0.3 mg/kg daily) has proven to be a useful chemopreventative strategy in the management of renal transplant recipients with widespread epidermal dysplasia and multiple NMSC (both SCC and BCC). Acceptance of a partial prophylactic effect using a well tolerated low dose of acitretin may be preferable compared with a higher dosage and the likelihood of inducing toxic side-effects that patients would not tolerate long-term [102,116].

Epithelial precancerous and cancerous skin lesions

Isotretinoin and calcitriol can exert antitumor effects in both in vitro and in vivo systems. Experimental data suggest that the synergistic action of these compounds could be due to the capability of retinoid and vitamin D nuclear receptors to form heterodimers, leading to enhanced transcription and biological effects. Multiple, multifocal precancerous and cancerous skin lesions were treated with combination of isotretinoin and calcitriol, with improvement of actinic keratosis and diminution in size of squamous and basal cell carcinomas. Oral isotretinoin is able to prevent the development of new tumors in Muir-Torre syndrome. Low-dose acitretin could prevent premalignant and malignant lesions in renal transplant recipients [117].

Kaposi sarcoma

Kaposi's sarcoma is a multifocal neoplastic process with four clinical variants; all of them are 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. Treatment of patients with alitretinoin gel resulted in a significant antitumor effect. Alitretinoin gel 0.1 % is approved for the treatment of cutaneous lesions of AIDS-associated Kaposi's sarcoma. In patients received treatment with alitretinoin gel twice daily for 12 weeks, patients tolerated 60 and 100 mg/m² per day. Most patients found 140 mg/m² per day intolerable owing to headache. Common treatment-related adverse events were headache, xerosis, rash, alopecia, and hyperlipemia. The median duration of treatment was 15.1 weeks. 9-cis-retinoic acid capsules have moderate activity and provide durable responses; however, substantial toxic effects at higher doses limit its suitability as an anti-KS therapy [118,119].

Keloid

Panabiere-Castaings (1988) reported nine females and two males with keloids were treated with 0.05% tretinoin topically for 12 weeks. Since retinoids affect collagen metabolism, changes in size were evaluated by serial kodachromes, tape measurements, and appreciation of volume using dental mouldages. A significant decrease in weight (p less than 0.04) and size (p less than 0.01) was found when comparing the status of the lesions at the beginning of the study and at week 12 [120].

Oral leukoplakia

The data from a few clinic studies demonstrate a significant therapeutic effect of 13-cis-retinoic acid in patients with oral leukoplakia; however, it cannot state whether the reversal of premalignant lesions will result in reduction of the incidence. Although direct application of higher concentrations of retinoic acid results in suppression of oral leukoplakias only, its use in the treatment of patients with recurrent and persistent lesions may be justified for controlling lesions that otherwise may progress. The mechanism of retinoids treat oral leukoplakia is related to restoration of the expression of RAR β mRNA, which was selectively lost in premalignant oral lesions and can be restored by treatment with isotretinoin. Vitamin A modulates growth and differentiation of cells, and its deficiency enhances susceptibility to carcinogenesis [121,122].

IV. Diseases of the genitalis

Erythroplasia of Queyrat

A male patient did not respond to laser therapy; despite repeated excisions over 4 years he presented with a relapse. The meatal cytology revealed dysplastic cells consistent with in situ carcinoma. Conservative treatment with isotretinoin was started for a period of 9 months. Clinically, there was a complete response after 3 months of treatment. Meatal cytology returned to normal after 5 months of treatment. However, 6 months after the end of the therapy, clinical signs reappeared and cytology confirmed recurrent disease. The phenotypic changes were slow in onset and not sustained to withdrawal of retinoids. These data suggest only temporary reversal of the phenotype and not eradication of the disease. Also, the relapsed lesion was invasive carcinoma [123].

Lichen sclerosus

52 male patients with severe, long-standing lichen sclerosus were randomized in a 2:1 ratio to receive daily acitretin (35 mg) or placebo for 20 consecutive weeks. Follow-up lasted for 36 weeks from baseline. The primary endpoint was complete response of active lichen sclerosus as well as improvement of patient quality of life. Acitretin is safe and effective for the management of severe, long-standing lichen sclerosus of the male genitalia [124]. Topical 0.025% tretinoin was applied once a day, five days a week, for one year. Topical tretinoin seems feasible for use in the topical treatment of vulvar lichen sclerosus [125].

V. Photoaging and disorders of pigmentation

Photoaging

In the treatment of aging, retinoids improve dermal functions by increasing fibroblast proliferation and collagen production and decreasing matrix metalloproteinase-mediated extracellular matrix degradation. Six months of once-daily applications of a 0.05% tretinoin emollient cream

specifically formulated for the treatment of photoaged skin is an effective therapy for improving fine wrinkling, mottled hyperpigmentation, and skin roughness associated with chronic sun exposure [126].

Actinic keratosis

Treatment with oral acitretin (10-50 mg/kg daily for 12 months) markedly decreases the lesions of actinic keratoses. Isotretinoin 0.1% cream cannot compete with more rapid treatments of actinic keratoses. However, its effect on facial lesions may be beneficial during long-term treatment of associated sun-damaged skin [127,128].

Confluent and reticulated papillomatosis of Gougerot and Carteaud

Retinoids are widely used in the treatment of photoaging to stimulate dermal repair. Treatment with oral isotretinoin 1 mg/kg/day for 14 and 18 weeks in combination with 10% lactic acid lotion (18 months) markedly decreases in pigmentation and thickness of the papules and plaques [129].

Hyperkeratosis of the nipple and areola

Hyperkeratosis of the nipple and areola is a rare disorder characterized by verrucous thickening and brown pigmentation of the nipple and areola. Surgical treatment has been suggested as an initial treatment in resistant and recurrent cases because of the relapses seen after medical treatment. Durmazlar reported a case that low-dose acitretin and topical calcipotriol treatment led to satisfactory response with no relapses during 2 years of follow-up [130].

Acanthosis nigricans

A woman was treated with oral isotretinoin and all lesions responded with flattening and a return to the normal skin. The patient received a maintenance dose because discontinuation of the therapy resulted in quickly recurrent lesions. Topical tretinoin and calcipotriol have also been used with some limited success [131,132].

VI. Granulomatous Diseases

Cutaneous sarcoidosis

A woman with cutaneous sarcoidosis was treated with isotretinoin, and a complete resolution of the skin lesions 8 months after the onset of treatment was observed. During the 15-month followup, the patient remained free of recurrence and of visceral involvement [133].

Disseminated granuloma annulare

Several reports detail the successful use of isotretinoin 0.5-1 mg/kg/day, primarily in the disseminated form of the disease. Temporary remission of disseminated granuloma annulare under oral isotretinoin therapy [134].

Perforating granuloma annulare

A woman with a painful eruption on the hands, elbows, and knees was treated with isotretinoin with nearly complete resolution of the lesions and with dramatic relief of pain. Cessation of treatment resulted in recurrence of some lesions during a 6-month period. Treatment with isotretinoin was begun with satisfactory control of the disease and fewer side effects. When treatment was stopped, a few lesions persisted, but no relapse was observed 6 months later [135].

Siliconoma

A woman developed protuberant facial granulomas 15 years after the injection of silicone fluid. She was treated with isotretinoin. Treatment with isotretinoin given orally in low doses (20 mg total dose per day) in low doses, with complete resolution of the granulomas [136].

O'BRIEN's actinic granuloma

Treatment with isotretinoin during 12 weeks prevented the development of new granulomata and produced almost complete resolution of established lesions in a 75-year-old man [137].

Annular elastolytic giant-cell granuloma (AEGCG)

A 72-year-old man consulted for annular plaques, some of which were atrophic, and papules that had been present for 2 years. The lesions involved sun-exposed and non-sun-exposed skin. The biopsies showed granulomatous infiltrates and discrete elastophagocytosis. After ruling out various differential clinical and histological diagnoses, the patient was diagnosed with AEGCG. We reported a case of AEGCG. Diagnosis was not easy. The differential diagnoses of this entity were discussed and we ruled out actinic granuloma, sarcoidosis, leprosy, and granuloma annulare. Our patient presented the classical annular variant combined with a popular variant. This is the first case involving response to isotretinoin [138].

Kyrle's disease

Baumer (1989) reported a 50-year-old woman having suffered from atypically located Kyrle's disease for 2 years. In particular, the palmoplantar areas were affected by keratotic erythematous papules showing the typical histologic picture of Kyrle's disease. Treatment with acitretin (initial dose 30 mg/day) resulted in almost complete remission after 6 months. A concomitant lichen nitidus remained unchanged [139].

VII. Infectious Diseases

Gram-negative folliculitis

Gram-negative folliculitis in acne and rosacea patients is best treated with isotretinoin (0.5-1 mg/kg daily for 4-5 months). The mechanism by which isotretinoin eliminates gram-negative bacteria appears to be secondary to ecologic changes because the skin and mucous membranes become dry. Thus,

the environment becomes inhospitable for gram-negative bacteria, which require moisture to survive and proliferate. Antibiotic therapy too frequently turned out to be indefinite in length, and relapses following discontinuation of therapy were the rule. In contrast, isotretinoin can induce sustained remissions [140].

Tuberculosis Cutis

The compound betamethasone acupoint injection combined with oral application acitretin 10mg/d antituberculosis drugs is an effective method on treating the tuberculosis [141].

Lupus miliaris disseminatus faciei

A patient with this condition was treated with oral isotretinoin, with a dramatic improvement in almost all lesions. A spontaneous involution with scarring is generally observed after a course of 12 to 24 months; however, the improvement 1 month after the beginning of the treatment suggests that isotretinoin alters the natural course of the eruption [142].

Fungal skin disease

The addition of isotretinoin appeared promising in the chronic inflammatory forms in treatment of tinea capitis [143]. Bartell (2006) described the incidental clearance of pre-existing tinea versicolor skin infection with the treatment of oral isotretinoin therapy for acne vulgaris [144].

Blastomycosis-like pyoderma

A dramatic response to combined treatment of low-dose acitretin (20 mg acitretin daily) and sensitive antibiotics has been achieved in a 23-year-old man with localized blastomycosis-like pyoderma. The duration of combined treatment was five months, and no recurrence was observed during the three month follow-up after discontinuing the drug treatment [77,145].

VIII. Warts

Verruca vulgaris, Verruca plantaris, Verruca planae

In immunosuppressed renal allograft recipients who are prone to develop extensive warts and verrucous keratoses, both oral etretinate and topical retinoic acid (0.01 to 0.05%) have been shown to be helpful in reducing the numbers of lesions.

A 20 year-old man employed as a waiter, presented with verrucous lesions over the face, palms and left lower limb for a duration of six years. Lesions began on the face and gradually spread to other parts of the body. The patient was treated with oral acitretin 0.5 mg/kg body weight/day for a total duration of three months. After three months of acitretin therapy, the lesions had completely flattened leaving hyperpigmented macules. No recurrence was seen during follow-up for six months after treatment [146]. A 22-year-old male patient who has with a history of multiple warts over his scalp was started on a systemic retinoid (acitretin 0.5 mg/kg once daily).

He was also treated with once weekly cryotherapy (with liquid nitrogen spray). At the end of 4 weeks, there was dramatic and complete clearance of the lesions with no recurrence. He continued on acitretin alone for a period of two more months. The patient has now been on follow-up for 5 months and there has been no recurrence of the lesions [147]. A 43-year-old white female affected by Epidermodysplasia verruciformis (EV) who developed multiple warts and cancer lesions harbored HPV 24 along with the novel putative HPV type FA51. The patient was treated with a combination of acitretin (0.2 mg/kg per day) and peginterferon alfa-2b (1 µg/kg per week s.c.) for one year, with marked improvement of verrucous lesions and no recurrence of mucosal cancer [148].

Condylomata acuminata

Oral isotretinoin may be regarded as an effective, fairly well-tolerated, and noninvasive alternative form of therapy for immature and small condylomata acuminata, randomly assigned to receive isotretinoin alone or isotretinoin and IFN α -2a. The combination of isotretinoin (0.5-1 mg/kg/day) and IFN α -2a achieves higher remission rates and a shorter duration of treatment than isotretinoin alone. These findings suggested that the inhibition of telomerase activity and arrest of cells at G0/G1 phase might be the key steps through which inhibits the proliferation of keratinocyte and others cells. Therefore, retinoids may have therapeutic potential to complement current treatments of CA [149]. Giant condyloma acuminatum (GCA) is a unique variant of condyloma acuminata. It carries a substantial risk of squamous cell carcinoma. Various treatments have been used, but response is often poor and recurrence rates are high. It is recommend that oral acitretin and topical imiquimod can be used in selected cases of GCA (large numbers and huge volume). These data demonstrate the central role of EGFR activation in retinoid-induced epidermal hyperplasia. We have hypothesized that the retinoid inhibition of cell proliferation may be due to the retinoid-dependent reduction in EGFR level. Retinoic acid regulates EGFR levels by independent effects on the EGFR promoter [150].

IX. Autoimmune Diseases

Cutaneous lupus erythematosus

Cutaneous manifestations of lupus erythematosus were treated with isotretinoin. Most of cases with the cutaneous lesions were resistant to conventional therapies. Acitretin showed dramatic and rapid improvement. However, a recurrence of cutaneous lesions, after the completion of the treatment, occurred as quickly as the initial improvement appeared [151]. A randomized, double-blind, multicentre study was performed to compare the efficacy of acitretin (50 mg/day) with hydroxychloroquine (400 mg/day) in 28 and 30 patients, respectively, suffering from cutaneous lupus erythematosus (LE). The present results demonstrate that both acitretin and hydroxychloroquine provide effective treatment in approximately 50% of cases of cutaneous LE. Acitretin was used in the treatment of 20 patients who had cutaneous lupus erythematosus [152]. In 15 patients, an excellent (total clearing) or good response (marked reduction of all lesions)

was seen usually within two to four weeks. It is concluded that acitretin is a highly effective and well-tolerated drug in the treatment of cutaneous lupus erythematosus [153]. Topical tretinoin can improve lesion [154].

Systemic sclerosis

Bilen (1999) reported a case of morphea and psoriasis that improved with acitretin treatment. He suggested that the improvement of the morphea lesions may be due to an immunomodulatory effect of the drug or a decrease in collagen production by dermal fibroblasts due to retinoic acid [155] Maurice (1989) reported another case of thirteen patients with systemic sclerosis treated with isotretinoin. Nine patients completed between 6 and 14 months of treatment and all showed an improvement in the cutaneous manifestations of their disease. Most patients experienced the well-recognized side-effects of retinoids, which in three cases necessitated withdrawal from the study within 3 months. There may be a preferential suppression of the synthesis of type I collagen, or the drug may be acting by an unrelated mechanism. During an open prospective study of the synthetic retinoid isotretinoin in ten patients with systemic sclerosis, one patient developed an eosinophilic pleural effusion and two patients were noticed to have asymptomatic deterioration in pulmonary function tests. The pulmonary function of all treated patients was then compared retrospectively with a similar control group of patients not treated with isotretinoin. There was a significantly greater decrease in the 1-s forced expiratory volume and transfer coefficient in the patients with systemic sclerosis being treated with isotretinoin in comparison to the untreated control patients. Studies of lung function in patients treated with isotretinoin for other indications are required [156].

X. Bullous dermatoses

Gruss (2000) reported a patient with subcorneal pustular dermatosis type of IgA pemphigus who rapidly responded to systemic treatment with isotretinoin. Systemic treatment with isotretinoin 20 mg daily led to complete clearance of skin lesions within 3 weeks. Isotretinoin was an effective drug in the treatment of subcorneal pustular dermatosis type of IgA pemphigus in this patient. Papular acantholytic dyskeratosis with oral isotretinoin acquired good results [157]. Yoo (1994) reported a case of a bullous variant of transient acantholytic dermatosis in a 59-year-old female. Each bullous lesion lasted several weeks and healed without scarring. The lesions were migratory and recurrent without a cleared period.

Histopathologic examination revealed an intraepidermal vesicle low in the epidermis. The lesions cleared after 2 months of isotretinoin therapy [158]. Patients with recessive dystrophic epidermolysis bullosa (RDEB) A total of 20 patients with RDEB aged 15 years or older were treated daily for 8 months with isotretinoin (with a targeted dosage of 0.5 mg/kg/d). Isotretinoin, at least up to a dosage of 0.5 mg/kg/d, may be safely used in patients with RDEB.

Although increased fragility may occur, patients tolerated this drug well and were receptive to its long-term use for possible chemoprevention of cancer.

However, whether such an effect will occur is yet to be proven [159].

XI. Abacterial pustulosis

A patient who was affected with acrodermatitis continua Hallopeau, acitretin monotherapy resulted in a complete clearance of pustulation at a dosage of 45 mg per day [160]. Starting daily dosages between 10 and 25 mg and stepwise escalation were associated with higher clinical efficacy and lower incidence of adverse events in comparison with higher doses and regimens rapidly reaching optimal dose. Acitretin appears to provide better efficacy in pustular psoriasis than in plaque-type psoriasis (PV) as a single agent treatment [161]. A 78-year-old Caucasian male patient presented with subcorneal pustular dermatosis in association with a monoclonal IgA/k gammopathy. 7 months later the patient became unresponsive to dapsone treatment and was changed to acitretin 35 mg/d, with good control of the lesions and symptoms in 2 weeks [162].

XII. Genodermatosis

Hailey-Hailey disease

Hailey-Hailey disease is an autosomal dominant skin condition characterized by waxing and waning painful and pruritic vesicles and plaques affecting the intertriginous areas. Its pathogenesis involves inherited abnormalities in a cutaneous calcium pump. Berger (2007) present a case of Hailey-Hailey disease in a 64-year-old man who was refractory to conservative management but improved dramatically over 6 months of oral therapy with 25 mg of acitretin daily. A potential mechanism is based on the influence of retinoids on epidermal differentiation and may involve cutaneous calcium homeostasis [163].

Xeroderma pigmentosum

Retinoid therapy has been demonstrated to protect effectively against the development of skin cancers in patients with XP, six of whom were given oral isotretinoin. The NK cell activity was not affected by low-dose isotretinoin, i.e. 0.5 mg/kg per day. However, higher doses of isotretinoin, e.g. 1.0 mg/kg per day, produced a significant decrease in NK cell function, at the same time reducing the frequency of development of skin cancers. Retinoid therapy may have a skin cancer preventing effect by enhancing other immune effector mechanisms or via epithelial cell differentiation. A 15-year-old boy with XP presented with multiple facial BCCs that was previously treated by surgical excision. Standard BCC treatments such as surgery are not ideal for patients with several facial BCCs because of the risk of scarring, and the patient refused further surgery. Three times weekly application of imiquimod 5% cream in combination with oral acitretin (20 mg daily for 4-6 weeks) was prescribed for him as an alternative. No adverse events were reported during treatment and all tumors had resolved at the 6-month follow-up visit, highlighting the therapeutic potential of imiquimod 5% cream [164].

Olmsted syndrome

A 17-year-old girl presented with genital, perigenital and perianal hyperkeratotic plaques extending to the thighs, palmoplantar keratoderma and nail dystrophy. A small erythematokeratotic plaque was localized below the lower lip, who was diagnosed Olmsted syndrome. Improvement of the palmoplantar and genital lesions was noted after one month of treatment with 25 mg acitretin daily. Thus, acitretin seems to be the treatment of choice of this syndrome in adults [165].

XIII. Lichenoid Diseases

Cutaneous lichen planus

A double-blind versus placebo trial was carried out in 65 patients with severe cutaneous lichen planus resistant to treatment with topical corticosteroids. Acitretin induced a significantly higher patient response rate than did placebo in particular in a rapid relief of pruritus. Overall, acitretin treatment led to remission or marked improvement in 64% to 83% of patients, and a beneficial effect was also observed on lichen planus of mucous membranes. Compared with the other current combination or single treatments of lichen planus, acitretin is the first-line therapy for cutaneous lichen planus. Seven patients whose lesions were resistant to other treatments received isotretinoin for painful oral lichen planus as well as generalized pruritic lichen planus, and good to excellent results during the treatment, which never exceeded 2 months, were obtained [74]. Among all systemic retinoids, only acitretin has shown a relatively good level of evidence of its efficacy in the treatment of cutaneous lichen planus [166].

Lichen amyloidosis

Two patients with lichen amyloidosis with typical clinical symptoms did not respond to local treatment. A combined regimen with bath psoralen ultraviolet A (PUVA) and oral acitretin was initiated, resulting in nearly complete resolution of the papules and impressive relief from the severe pruritus. The beneficial response has persisted for 8 months. The suggested combined therapy with bath PUVA photochemotherapy and oral acitretin represents an efficacious and practical treatment modality for lichen amyloidosis with long-lasting effects [167]. A 57-year-old Vietnamese woman has had extensive generalized recalcitrant lichen amyloidosis for 23 years. Treatment with oral etretinate (25 mg/day) for 3 years, and later oral acitretin (10 mg/day) for the past 10 years, has controlled the pruritus and flattened the hyperkeratotic papules. Whenever the acitretin was ceased her symptoms flared within weeks. On each occasion reintroduction of acitretin was effective within 1-2 months. The second case is that of a 51-year-old Australian Aboriginal woman who had a 2-year history of lichen amyloidosis affecting her lower legs. A 2-month course of oral acitretin (25 mg bid.) produced a marked improvement in both the pruritus and hyperkeratotic papules.

She was then lost to follow up for 2 years, during which time her symptoms recurred [168].

XIV. Skin Appendages and Other Organs

Hair

Very few studies have performed for testing the efficacy of topical tretinoin in alopecia areata. Sudip Das's study did show a reasonable good response in 55% patients [169]. Topical tretinoin showed insignificant response when applied for 3 month period. Topical all-trans-retinoic acid (tretinoin) alone and in combination with 0.5% minoxidil has been tested for the promotion of hair growth in 56 subjects with androgenetic alopecia. After 1 year, the combination of topical tretinoin with 0.5% minoxidil resulted in terminal hair regrowth in 66% of the subjects studied. Tretinoin was shown to stimulate some hair regrowth in approximately 58% of the subjects studied [170]. One female subject with pronounced alopecia for more than 20 years had hair regrowth by using only tretinoin for a period of 18 months. Tretinoin has been shown to promote and regulate cell proliferation and differentiation in the epithelium and may promote vascular proliferation. These factors are important for hair growth promotion. These preliminary results indicate that more work should be done on the role of retinoids in hair growth. The synergistic effect of retinoids in combination with a low concentration of minoxidil should also be further investigated [171]. All-trans retinoic acid induces premature hair follicle regression (catagen) by upregulation of TGF β 2 in the dermal papilla. Diffuse hair loss ranks among the most frequent and psychologically most distressing adverse effects of systemic therapy with retinoids, which severely limits their therapeutic use even where clinically desired. Oral tretinoin and extra use appear obvious different responses on hair growth. TGF-2 has been shown to exert hair growth promoting effects during morphogenesis; in contrast, TGF-1 and TGF-2 are recognized as potent catagen inducers in murine and human anagen. Therefore, It hypothesized that TGF- may act as a mediator of retinoid-induced hair growth inhibition. studied ATRA upregulates TGF-2 inhibiting hair growth. Whether topical use RA irritate hair growth or not was misunderstanding [172]. Seckin reported one case to emphasize that acitretin can be added to the list of drugs that induce changes in hair colour and texture. A 70-year-old woman with psoriasis who noticed darkening of her previously white hair, which also gained a curly appearance after 6 months of acitretin treatment [173].

Nail

Nail involvement occurs in up to 78% of patients with psoriasis, is more common in patients with psoriatic arthritis, and may be the only sign of psoriasis. The nail plate is composed of hard, translucent, dead keratin [174,175]. Therapy consisted of acitretin, 0.2 to 0.3 mg/kg/d, for 6 months should be considered in the treatment of nail psoriasis. Sánchez-Regaña reported that significant reductions were found received antipsoriatic classical treatment (acitretin, methotrexate, cyclosporin, PUVA,

NUVB, REPUVA, RENUVB) except NUVBA and received biological treatment (infliximab, efalizumab, etanercept, adalimumab) in nail psoriasis patients [176].

Geographic tongue

Lesions of the oral mucosa are frequently described in association with psoriasis, particularly in the pustular type. Controversy surrounds the question whether mucosal lesions can be considered as oral manifestation of psoriasis. Two patients presented with concurrent pustular psoriasis and mucosal lesions with the characteristic picture of geographic tongue. There was parallel improvement of the skin and the mucosal lesions with systemic retinoid treatment [177].

XV. Extracellular Matrix Alterations

Follicular mucinosis

A male patient was treated with oral isotretinoin, which led to a dramatic improvement of the skin lesions [178].

Scleromyxedema

Lominska-Lasota reported a 56-year-old male patient suffering from scleromyxedema was successfully treated with isotretinoin (13-cis retinoic acid, Roaccutan). After 10 months therapy, we observed considerable reduction of the cutaneous infiltration and the skin thickening; the papular eruptions had almost completely disappeared. The mobility of the joints, however, could only be slightly improved [179].

Striae distensae

The experience of 20 patients with striae distensae of varying etiologies and the treatment with topical tretinoin is described. Of the 16 patients who completed the study, 15 had significant improvement in their clinical picture [180].

CHILDREN SKIN DISEASE

Retinoids, as „marvelous drugs”, have important untoward effects besides their therapeutic properties that may be deleterious during the growth and development of the human being from gestation to adolescence. Children, like adults, generally tolerate short-term retinoid therapy without major complications.

Ichthyosis and ichthyosiform dermatoses

The genetic disorders of keratinization represent a large and heterogeneous group of hereditary dermatoses. The various forms of ichthyoses are classified according to their mode of inheritance, clinical and pathologic features, and basic defect. The most severe forms are represented by the so-called true ichthyoses: lamellar ichthyosis, nonbullous congenital ichthyosiform erythroderma, bullous ichthyosis (also called epidermolytic hyperkeratosis), and the transitory forms harlequin fetus and collodion baby [59,181].

Harlequin ichthyosis (HI)

Because of its rarity and the short-life span of most affected infants (6 weeks or less), these infants can survive with neonatal intensive care and retinoid therapy and need long-term interdisciplinary treatment in order to improve quality of life [182].

Lamellar Ichthyosis (LI)

The management of LI has drastically changed since the introduction of the oral synthetic retinoids. Even if they do not revert the keratinization defect, retinoids considerably alleviate the hyperkeratotic component, turning the skin almost normal. However, the lesions promptly regress after discontinuation of therapy. Careful monitoring of the LI children and a dose of no more than 1 mg/kg/day of long-term etretinate therapy does not appear to represent a substantial risk for major adverse effects and can be given to children with an acceptable margin of safety. Acitretin was given as a treatment dose of 0.77-1.07 mg/kg x per day (mean 0.86+/-0.11) and maintenance dose of 0-0.94 mg/kg x per day (mean 0.33+/-0.26) to 28 children with severe inherited disorders of keratinization. Body height and weight were chosen as the monitoring indexes to evaluate the growth and development and other common side effects as the safety evaluation of the children for a follow-up of 2-36 months. Acitretin showed a satisfactory therapeutic effect on severe inherited disorders of keratinization in children [59,69,183,184].

Nonbullous Congenital Ichthyosiform Erythroderma (NBIE)

Therapy of NBIE is similar to that of LI. Topical emollients and keratolytic agents partially control the desquamation. The majority of these patients require long-term etretinate or acitretin therapy to maintain their skin free of lesions. Newborn infants with nonbullous ichthyosis form erythroderma, who presented at birth with a collodion baby appearance, were treated with acitretin (1 mg/kg/day). Clinical improvement was achieved shortly after treatment. Baby received oral retinoid for 3.5 months and was followed for nine months. The treatment resulted in a satisfactory improvement in the skin condition of the first case. The tolerance to the drug was good [185].

Collodion Babies (CB)

These babies have an increased perinatal morbidity and mortality both from their prematurity and their abnormal skin. Topical treatment with tazarotene 0.1% gel resulted in rapid improvement [186].

Epidermolytic Hyperkeratosis (Congenital Bullous Ichthyosiform Erythroderma or Bullous Ichthyosis)

Disseminated and generalized hyperkeratotic forms of EH have been treated with lower dosages of oral retinoids than those used for LI.

Keratitis ichthyosis deafness (KID)

Xibao-Zhang (2006) reported 3 cases KID syndrome children, started on treatment after the age of 15 years, and had an excellent response to a high dose of acitretin (>0.8 mg/kg per day). The maintenance dose was titrated down to the lowest effective level of 0.2 mg/kg per day [187].

XV. Other disorders of keratinization

Palmo-plantar keratoderma

Children with this disorder may be treated with retinoids. Etretinate and acitretin are effective in the treatment of PPK, with a good to excellent response. Generally, hyperkeratotic lesions desquamate or detach in large sheets after 2 to 3 weeks of therapy, leaving behind a red, finely scaled, and tender surface, requiring emollients and hydration special care. Loading dosages range from 0.5 to 1 mg/kg/day given in a single daily dose. Maintenance therapy must be individually adjusted according to efficacy and occurrence of adverse reactions. Treatment with low dosages (0.2 to 0.5 mg/kg/day) may be given continuously or periodically depending on clinical response and tolerance [59,179,188].

Pityriasis Rubra Pilaris

All clinical forms of PRP show marked improvement with isotretinoin and etretinate at dosages of 1 to 1.5 mg/kg/day. For self-limited cases, the natural evolution time (3 months to 7 years) shortens to 2 to 3 weeks with no recurrences. In chronic cases, a maintenance dosage (0.3 to 1 mg/kg/day) during 4 to 6 months is required. Generally, no severe relapses occur for a longer period of time after the end of therapy [59,188,189].

Darier's Disease

Oral retinoids (isotretinoin, etretinate, and acitretin) are specific therapeutic agents for Darier's disease. However, in children only severe cases may be treated with oral retinoids. Clinical improvement is observed after 2 to 4 weeks of therapy, but lesions usually relapse 2 to 3 weeks after discontinuation of therapy. Low initial dosages of 0.2 mg/kg/day may be gradually increased to 0.5 to 1 mg/kg/day depending of the therapeutic response. Lesions slowly clear, even in cases resistant to conventional therapies. A maintenance dosage of 0.20 to 0.50 mg/kg/day is generally sufficient to keep the patient controlled with the minimum long-term side effects [59,189].

Psoriasis

Pediatric patients may present with severe forms of psoriasis failing to respond adequately to conventional therapy, and because alternative therapies such as PUVA, cytotoxic drugs, and cyclosporine may have serious side effects, treatment with oral retinoids must be considered in some case. Extensive recalcitrant pustular or erythrodermic types of psoriasis are often candidates for oral retinoid therapy.

Although isotretinoin has been used in the treatment of psoriasis, etretinate is clearly superior; however, oral therapy with isotretinoin at high dosage levels of 1.5 to 2 mg/kg/day cleared generalized pustular psoriasis [189]. Etretinate and acitretin show little difference in their therapeutic effects, and both can be considered for initial treatment of children with intractable, severe forms of psoriasis that seriously impair quality of life. Pustular types of psoriasis respond in a few days to dosages of oral retinoids in the range of 0.75 to 1 mg/kg/day. Erythrodermic types respond better to lower dosages of 0.3 to 0.5 mg/kg/day. The dosage must be gradually reduced depending on response or severity of side effects. Therapy should be continued for 1 or 2 months after complete clearing of skin lesions [189,190].

Acne

If treatment with isotretinoin starts only when other treatment options have failed, acne will be cured, but it will be too late to prevent permanent scarring. Severe recalcitrant infantile acne may also require isotretinoin therapy. Isotretinoin is an expensive medication; however, when compared with the cost of years of antibiotics and consultations, the cost-benefit advantage of isotretinoin therapy becomes evident. The dose of isotretinoin used should be considered in terms of daily dosage and in terms of total dosage. The amount of daily

dosage is related more to side effects than to therapeutic efficacy since low dosages have a similar therapeutic effect as high dosages. The total treatment dosage is related to probability of acne relapse. Total dosages lower than 100 mg/kg to 120 mg/kg are associated with a higher risk of acne relapse. In children and in adolescents we prefer to use a low daily dosage of 0.3 mg/kg to 0.5 mg/kg for a longer period of time (6 to 12 months) instead of higher dosages for a shorter time span [59,191].

XVI. Other Uses

Systemic retinoids (isotretinoin, etretinate, and acitretin) have been shown to be effective chemotherapeutic agents in studies of patients with xeroderma pigmentosum, the nevoid basal cell carcinoma syndrome, and recipients of organ or bone marrow transplantation. In children, retinoids have been used in genodermatoses with high risk of cutaneous malignancies such as xeroderma pigmentosum, epidermodysplasia verruciformis, and nevoid basal cell carcinoma syndrome. Isotretinoin (2 mg/kg/day) reduced the tumor frequency during the period of treatment from 12 basal cell and squamous cell carcinomas per year to 2.5 tumors per year. After treatment, tumors frequency returned to pretreatment level or greater.

Systemic retinoids		
Substance	Off-label Indications	Selected dose
Acitretin	Hidradenitis suppurativa	0.3-0.5mg/kg daily [87,88]
	Nodulocystic acne (resistant to other treatments)	0.3-0.5mg/kg daily [87,88]
	Infant acne	0.3-0.5mg/kg daily [87,88]
	Hyperkeratotic hand eczema	30 mg daily [76,77]
	BCC and SCC	2mg/kg daily [101,102]
	Cutaneous t-cell lymphoma	25-50mg daily [106,108,109]
	Hailey-Hailey disease	25 mg daily [163]
	Cutaneous lichen planus	10-30 mg daily [166]
	Lichen amyloidosis	10-50 mg daily [168]
	Psoriasis nail	0.2-0.3 mg/kg daily [176]
Isotretinoin	Pustular psoriasis	2mg/kg daily [70,71]
	Lamellar ichthyosis	0.5-1.0mg/kg daily [72]
	Solid facial edema	0.5mg/kg daily [91]
	Rosacea	0.5 mg/kg daily [90]
	Steatocystoma multiplex	1mg/kg daily [92]
	Eosinophilic pustular folliculitis	1mg/kg daily [97]
	BCC and SCC	30-50 mg/kg daily [101,103]
	Metastatic melanoma	1-2mg/kg daily [105]
	Xeroderma Pigmentosum	0.5-1.0 mg/kg daily [164]
	Confluent and reticulated papillomatosis of Gougerot and Carteaud	1.0 mg/kg daily [129]
	Cutaneous T-cell lymphoma	1.0-2.0 mg/kg daily 105,109]

Table III. Off-label uses of retinoid and Indications (scattered case reports)

Low dosages of isotretinoin (0.5 mg/kg/day) reduce the tumor frequency, but not as much as with higher dosages. Etretinate and acitretin at a dosage of 1 mg/kg/day are good tumor preventive alternatives in xeroderma pigmentosum by dramatically reducing the incidence of malignant degeneration [192-194].

Good therapeutic results, though without complete remission, have been achieved with etretinate in epidermodysplasia verruciformis associated with HPV-3, HPV-5 and HPV-8 types. The effect of etretinate is probably dose-dependent; 1 mg/kg/day would appear to be sufficient. It has been suggested that retinoids indirectly inhibit viral replication owing to their action on keratinization [195].

Nevoid basal cell carcinoma syndrome is probably one of the most important indications for oral retinoids as chemoprophylactic agents. A dosage of 1 mg/kg/day seems to be suitable to prevent new lesions from appearing and to arrest the growth of older lesions by inducing differentiation. In summary, retinoids are effective as chemotherapy or chemoprevention; unfortunately, high dosages and continuous administration are required [196].

Conclusion

Retinoids are definitely effective in severe acne, certain forms of psoriasis and other disorders of keratinization - all diseases for which there has been no satisfactory treatment. Further clinical trials find that treatment of retinoids have acquired good effects in others skin diseases. Better knowledge of the long-term side effects will determine its exact role. Retinoids with greater specificity for target organs and fewer systemic side effects are being developed by means of modification of the basic structures. Possible future appearance of new retinoid compounds, with much more highly receptor-selective, effective and less toxic alone or in combination with other drugs may provide therapeutic solutions for benign and malignant proliferative skin diseases. Additional work will standardize the dosage and time course of treatment of retinoid on correspond skin diseases.

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