Title
Systemic retinoids in the management of ichthyoses and related skin types.

Journal
Dermatologic Therapy, 26(1)

Authors
Digiovanna, John
Milstone, Leonard
Schmuth, Matthias
et al.

Publication Date
2013

DOI
10.1111/j.1529-8019.2012.01527.x

Peer reviewed

Published in final edited form as:
Dermatol Ther. 2013 ; 26(1): . doi:10.1111/j.1529-8019.2012.01527.x.

SYSTEMIC RETINOIDS IN THE MANAGEMENT OF OF ICHTHYOSES AND RELATED SKIN TYPES

John J. DiGiovanna[1], **Theodora Mauro**[2], **Leonard M. Milstone**[3], **Matthias Schmuth**[4], and **Jorge Toro**[5]

[1]DNA Repair Section, Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892

[2]Department of Dermatology, San Francisco Veterans Administration Medical Center, San Francisco, CA and Department of Dermatology, University of California, San Francisco, CA

[3]Department of Dermatology, Yale University School of Medicine, New Haven, CT

[4]Department of Dermatology and Venereology, Innsbruck Medical University, Austria

[5]Department of Dermatology, Washington DC Veterans Administration Medical Center, Washington, DC and Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD

Abstract

The term retinoid includes both natural and synthetic derivatives of vitamin A. Retinoid containing treatments have been used since the early Egyptians ~1550BC. Treatment of ichthyosiform disorders with retinoids dates back at least to the 1930's. Early use of high dose vitamin A demonstrated efficacy but, because vitamin A is stored in the liver, toxicity limited usefulness. Interest turned to synthetic retinoids in an effort to enhance efficacy and limit toxicity. Acetretin, isotretinoin and, in the past etretinate, have provided the most effective therapy for ichthyosiform conditions. They have been used for a variety of ages, including in newborns with severe ichthyosis and for decades in some patients. Careful surveillance and management of mucous membrane, laboratory, skeletal, and teratogenic side effects has made systemic retinoids the mainstay of therapy for ichthyosis and related skin types.

Keywords

ichthyosis; retinoid; isotretinoin; acitretin; ectropion

INTRODUCTION

The ichthyoses and related skin types include a broad spectrum of conditions which vary in etiology (inherited versus acquired), onset (congenital to adult onset), intensity (mild to severe), and extent of involvement (confined to the skin versus multisystem). The feature that all of these disorders have in common is abnormal cornification (keratinization). There may be abnormality in the quality and quantity of scale, the process of epidermal maturation (differentiation), the quality and quantity of stratum corneum, and the kinetics of keratinocyte proliferation. In most, the barrier function of the skin is abnormal.

Diagnosis is usually established by characterization of clinical features, inheritance pattern and associated findings. Therapy is usually multidimensional including hydration, lubrication and keratolytic agents that may be topical and systemic, and are directed at minimizing local symptoms or inducing remission.

Retinoid therapy has been known since the time of the ancient Egyptians, and Ebers Papyrus dated approximately ~1550BC discusses the use of ox liver, which is rich in Vitamin A, as a treatment for night blindness. Vitamin A deficiency was related to epithelial changes in 1925 by Wolbach & Howe(1) and to cancer in 1926 by Fujimaki(2). Pityriasis rubra pilaris is one of the conditions that helped identify a relationship between retinoids and the disorders of cornification, and suggested that retinoids could offer a therapeutic option. Long before a molecular basis of retinoid action was understood, Griffiths(3) wrote about a 1931 report by Frazier and Hu(4) ascribing cutaneous changes to vitamin A deficiency in Chinese soldiers from Peiping Province. In 1935, Loewenthal(5) noted that similar changes in prisoners in Uganda were histologically similar to those of PRP and could be treated with cod liver oil, a rich source of vitamin A. In 1941, noting similarities in keratotic papules seen in vitamin A deficiency and Darier disease, Peck, Chargin and Sobotka reasoned that the dyskeratosis of Darier disease might be related to vitamin A deficiency, and reported improvement with large oral doses of vitamin A.(6)

Currently, topical and systemic retinoids are widely used in the treatment of skin disorders and in the treatment and prevention of cancer. This manuscript will focus on the use of systemic retinoids in the management of ichthyosis and related skin types.

MANAGEMENT OF THE DISORDERS OF CORNIFICATION

The main features of ichthyosis are scaling and often thickening of the skin, and the main objects of treatment include hydration, lubrication, and removal of thick scale (keratolysis). (7) Even when thick, ichthyotic skin has an abnormal barrier function and increased transepidermal water loss. Humidification with long baths can hydrate and facilitate scale removal by abrasives such as sponges, etc. Lubrication with bath oils or after bathing to wet skin helps prolong skin hydration and flexibility. Lubricating agents vary and include lotions, creams, oils and ointments. Humidification of environments is also beneficial. Use of keratolytic agents facilitate desquamation and can include urea, salicylic acids and alpha hydroxy acids. Sometimes these are used under occlusion for enhanced effect. Care should be taken in children with agents such as topical salicylic acid because of absorption, and in conditions such as Netherton syndrome, in which the combination of the abnormal barrier and dermatitis can increase the absorption of topical medications such as calcineurin inhibitors (tacrolimus, pimecrolimus) and corticosteroids. In disorders with increased risk of skin infection such as epidermolytic hyperkeratosis, topical and systemic antimicrobials are often required. Topical modalities should not be discontinued when starting systemic retinoid therapy because they may allow synergistic benefit and can help to minimize toxicity by permitting lower oral dosing to be effective and by allowing retinoid holidays.

CONSIDERATIONS IN STARTING SYSTEMIC RETINOID THERAPY: WHO, WHEN, WHICH, AND HOW

Patient Selection

Before retinoid therapy is considered, it is important to thoroughly discuss the expected outcome and the potential adverse effects with the patient or, in the case of children, both the child and parents. Nearly all patients with ichthyosis get phenotypic improvement on systemic retinoids (Netherton is the main exception). Improvement generally occurs within several weeks to a month, but the scaling recurs if the retinoid is stopped. General reduction in the thickness of scale can be expected. For those who fatigue easily because of overheating secondary to absent sweating, systemic retinoids may increase the ability to sweat, an important benefit. Retinoids can significantly ameliorate ectropion or pseudoainhum. The side-effects or risks of long-term retinoid use includes the development of ligamentous calcifications, which occasionally are symptomatic, but are otherwise the

same as for short-term use; all are reversible except for the teratogenicity and skeletal changes. Because retinoids can affect growing bones, including epiphyseal fusion, initiation of retinoid treatment should be delayed as long as practical. Age, severity, time spent grooming, psychosocial status, and ability to understand/comply with contraception are important considerations before initiating retinoids. A trial on a systemic retinoid to measure efficacy is sometimes useful in helping the physician and patient balance the benefit/risk ratio. Retinoids cause a generalized keratolytic effect, which can abruptly lead to extensive shedding or peeling of scale. In epidermolytic ichthyosis, high doses can enhance blistering. A low dosage of retinoid should be prescribed initially, with a gradual increase in dosage until a satisfactory benefit is achieved.

Choice of Retinoid

Isotretinoin was initially developed as a synthetic retinoid, but this 13-*cis* isomer of naturally occurring tretinoin (*trans*-retinoic acid) is also present in cells as a naturally occurring metabolite. Both agents are structurally related to vitamin A. Etretinate (which is no longer available in the U.S., Canada and many European countries) is an aromatic retinoid which is slowly eliminated from the body(8). Acitretin is a metabolite of etretinate and has the advantage that it is not stored in adipose tissue and, therefore, has a half life of two days in humans. Etretinate is about 50 times more lipophilic than acitretin, and has a longer half-life (which can be as long as 120 days). Etretinate has been detected in the blood for up to 2 years after discontinuation of therapy, whereas acitretin becomes undetectable after 3–4 weeks. One of the greatest effects of either retinoid is the decrease in scaling and reduction of hyperkeratosis.

Responses and risks of isotretinoin and acitretin as treatments for ichthyosis are generally similar. Some patients think results with one are better than the other, but no consistent preference is clear. Acitretin, similar to its predecessor etretinate, has a greater capacity to cause peeling of the palms and soles compared to isotretinoin. A major advantage to long-term use of isotretinoin is its short half-life, simplifying dose changes, “drug holidays” and family planning. While isotretinoin is cleared within several months, acitretin has the potential to persist in the body because of conversion to etretinate, particularly when taken with ethanol. Therefore pregnancy should be avoided for 3 years following acitretin therapy(9). All currently available retinoids are teratogens, and require thorough discussion of this issue prior to and, repeatedly, during therapy. While perfect contraceptive measures are desirable, the possibility of an unintended pregnancy should be discussed. A US Food and Drug Administration–mandated registry (iPLEDGE) is now in place for all individuals prescribing, dispensing, or taking isotretinoin. This registry aims to further the public health goal to eliminate fetal exposure to isotretinoin.

Dose and Duration

The goal of choosing a dose should be to find the lowest dose that the patient finds acceptable. Few require more than 1 mg/kg of isotretinoin or 0.5 mg/kg of acitretin. Many patients find that considerably lower doses make a substantial difference in the way they look, feel, and in the time needed for grooming. Some patients even take “retinoid holidays” during the more humid summer months. For patients with Darier disease and epidermolytic ichthyosis, frequent adjustments of dose are common because for them the therapeutic window is narrow. Reports of long term safe use of retinoid therapy have been published and we have had patients who have taken systemic retinoids safely for decades.(10–12) However, most patients on long-term oral retinoids will develop diffuse skeletal hyperostosis, which will be asymptomatic in some, but cause significant back stiffness and/or hyperostoses in others.(13)

Toxicity

Therapy with systemic retinoids is associated with both acute and chronic toxicities. Mucocutanous toxcities of cheilitis, xerosis, dry nose, and eye irritation are common. Hair loss is more common and severe with acitretin compared to isotretinon, but is reversible after discontinuation of therapy. Alteration in hair texture, with development of curly hair has rarely been reported and may not be reversible. Laboratory abnormalities may be observed in blood cell counts, chemistries, and lipids.

Chronic toxicities mainly affect the skeletal system with an enthesopathy similar to diffuse idiopathic skeletal hyperostosis (DISH). This is manifested as hyperostoses or spurs along the spine (usually anterior spinal ligament) and at tendon and ligamentous insertions around joints (tendon and ligament calcification).(13)

Laboratory Monitoring

Before initiating oral retinoid therapy laboratory tests should be obtained, including a baseline complete blood count, chemistry panel which includes liver function tests, fasting triglyceride and cholesterol levels, and for females of child-bearing potential human chorionic gonadotropin (HCG). Frequency of follow-up depends on previous findings. HCG in women of child-bearing potential is repeated monthly. Other labs are rechecked at periodic intervals. During long term therapy, even when results are normal, most practitioners repeat labs every 3–12 months.

As soon as the patient decides that long-term therapy is well tolerated and will be desirable, a series of baseline radiographs are usually obtained. This usually includes lateral cervical, thoracic and sometimes lumbar spine, and may include the hips and lateral view of the calcanei of the feet, common areas of involvement with hyperostoses. Baseline bone density scan can also be performed at this time to determine the status of bone density. Frequency of follow-up depends on previous findings. If asymptomatic during the first few years we often repeat X-rays and bone density at 1–3 year intervals. If there are no changes or symptoms, some practitioners subsequently repeat imaging less frequently. Because extra-osseous calcification is associated with retinoid treatment, bone density measurements must be interpreted with caution.

MECHANISMS OF RETINOID ACTION

Retinoids act as ligands for nuclear transcription factors that control gene expression(14;15). Retinoids bind to different combinations of retinoid receptors, including retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Each of these has three different isotypes (alpha, beta, gamma). Upon RA binding, the ligand-receptor complex enters the nucleus and binds to specific DNA-binding elements present in promoters of genes. A number of co-regulatory proteins are recruited to the DNA-binding complex. The levels of these co-regulators are crucial for nuclear receptor-mediated transcription and many co-regulators have been demonstrated to be targets for diverse intracellular signaling pathways and post-translational modifications. Additionally, retinoid effects can also be mediated by direct interactions between the receptor and other cellular proteins, independent from DNA-binding. Through different combinations of these regulatory mechanisms, retinoids are able to modulate keratinocyte function(16), explaining why different retinoids can exert differential effects.

Regulatory elements within the promoter regions of target genes assure specificity by containing highly conserved repeats of sequences related to AGGTCA, with the spacing between the two motifs determining the choice of RXR partner. Differentially spaced half-site DNA elements produce distinct transcriptional responses. The DNA-binding domains of

the receptors undergo conformational changes when binding to the response elements; i.e., the receptors adopt different conformations at different binding sites. Ultimately, nuclear receptor binding results in the transcription of messenger RNA of downstream genes that subsequently become translated into a respective protein to produce a physiological response.

While retinoids were used therapeutically in clinical dermatology before the discovery of the nuclear retinoid receptors, a better understanding of underlying molecular pathways helps understand their broad spectrum of efficacy and toxicity. Retinoids can induce the expression of differentiation markers and exhibit inhibitory effects on keratinocyte proliferation in vitro(17;18). In other circumstances, retinoids stimulate epidermal proliferation with little effect on the expression of keratinocyte differentiation markers in vivo(19–21). In addition, retinoids have anti-inflammatory effects in skin disease(22;23).

RETINOIC ACID METABOLISM BLOCKING AGENTS

In addition to modulation by exogenous administration of RA, keratinocyte differentiation can be affected by alterations in the intracellular concentrations of RA(16). Retinoic acid (RA) can be synthesized from retinol taken up from the circulation.(24) In the peripheral blood, the availability of retinol is regulated by retinol-binding protein (RBP). STRA6 (stimulated by retinoic acid) protein is a membrane receptor, mediating retinol uptake into cells. Cellular retinol binding proteins (CRBP I & II) bind intracellular retinol. Intracellular retinoid concentrations are controlled by: i) dehydrogenases involved in RA synthesis (RalDH2, RoDH-4); ii) lecithin:retinol acyl transferase (LRAT), acyl CoA:retinol acyl transferase (ARAT), and GS2(25–27), which mediate esterification with long chain fatty acids; and iii) CYP26, which degrades RA.

CYP26 inhibitors, also termed retinoic acid metabolism blocking agents (RAMBAs) can alter intracellular RA concentrations. CYP26 inhibition represents an alternative way of increasing retinoid bioavailability within the epidermis(27). While RAMBA inhibition has similar effects on the epidermis as RA administration itself(28), the hope is that modulating RA metabolism rather than exogenously adding RA to the organism limits adverse effects. RAMBAs preferential exert their effects in specific target tissues (e.g., the epidermis) and they are quickly eliminated after treatment has been stopped. Retinoid-independent effects may also contribute to an improved benefit/risk ratio of RAMBA over the exogenous administration of RA.

The first RAMBA was the antifungal ketoconazole. The imidazol derivative, liarozole, which lacks antifungal activity, has received orphan drug status for congenital ichthyosis from the European Commission and from the US Food and Drug Administration (FDA). RAMBAs are not currently approved in the U.S.

DISEASE SPECIFIC CONSIDERATIONS

Ichthyoses

Autosomal Recessive Congenital Ichthyosis—The clinical presentation and severity of autosomal recessive congenital ichthyosis (ARCI) may vary significantly, ranging from harlequin ichthyosis (HI), the most severe, to lamellar ichthyosis (LI), and then to nonbullous congenital ichthyosiform erythroderma (CIE). While the clinical hallmark of ARCI is epidermal scaling, patients may also have a collodion membrane at birth, ectropion, eclabium, alopecia, palmoplantar keratoderma, hypohidrosis, and/or variable erythema. Patients with LI have large, dark, plate-like cutaneous scales with minimal erythema, while patients with CIE have erythroderma with overlying fine white scales. LI and CIE both have

their own clinical spectrum within ARCI. Causative mutations have been identified in eight genes: *TGM1*, *ALOX12B*, *ALOXE3*, *ABCA12*, *NIPAL4* (ichthyin), *CYP4F22* and *LIP*. Mutations in *TGM1* account for 50%–60% of all ARCI and most patients with LI. Individuals with HI have mutations in *ABCA12*, which has also been described in some LI *pts*. Mutations in *ALOXE3*, *ALOX12*, *NIPAL4 and PNPLA1* are present in NCIE or intermediate LI/NCIE phenotypes(32–35).

Retinoids have been reported efficacious in the treatment of ARCI based on case reports and series(5–11, 36–41). In many patients marked improvement or remission has been reported as long as the drug is continued, which for many patients has spanned decades (Fig 1a–c). The mechanism of retinoid action in ARCI likely involves modulation of keratinocyte differentiation, keratinocyte hyperproliferation, and tissue infiltration by inflammatory cells. Systemic retinoids used in the treatment of ARCI include isotretinoin, acitretin and etretinate.

Acitretin therapy markedly improves most patients with LI/CIE. The optimal dose varies considerable among individuals, but responses usually fall into high and low dose profiles(41). Most patients with classical manifestations of LI improve markedly, and the remaining patients show mild to moderate improvement. Some patients improve after a gradual incremental increase in dosage (≥ 35 mg/day). In these patients the maximum dose is limited by mucocutaneous side effects (cheilitis, epistaxis or hair loss). Other patients, including with the erythrodermic variant, notice marked deterioration in their skin condition with dosages ≥35 mg/day, but improve with low-dose acitretin treatment (10–25 mg/day) (41). Cosmetically acceptable hair re-growth has been described in a patient with severe alopecia after 4 years of oral retinoid therapy(41). Aromatic retinoids (acetretin, etretinate) have a more pronounced response on volar skin in the treatment of palmoplantar hyperkeratosis, with greater shedding of thick palms and soles. While acitretin (0.5–1 mg/kg/day) is more commonly used than isotretinoin, isotretinoin has a shorter half-life and, therefore, poses a lower teratogenic risk for females of child-bearing potential.

In ARCI, skin thickness and scaling decrease with retinoid therapy beginning about 1–2 weeks after the initiation of therapy. Thickening recurs after the retinoid is discontinued (Fig. 1d). Compared with LI, some patients with CIE may respond more completely and at lower doses. Since the systemic retinoid therapy is likely to be used long-term, it is wise to keep the dose as low as is practical, to employ retinoid-free periods (retinoid holidays) and to encourage the use of topical therapy to reduce the dose of retinoid required. While blepharitis and conjunctivitis are well-known retinoid side-effects, these drugs are usually well tolerated by patients with ectropion(37). Systemic retinoids have the ability to decrease the tendency for ectropion to progress. Patients with ectropion should pay careful attention to eye care, with artificial tears and eye lubricants, since lack of eye lubrication can lead keratitis, and regular ophthalmology evaluation is recommended (see Complications of Ichthyosis Beyond the Skin). The retraction of the lids is a concern at night when failure of the lids to close during sleep can lead to exposure keratitis. Topical ophthalmic ointments at bedtime can minimize problems.

Inhibitors of cytochrome P450 (CYP) 26, the rate-limiting enzyme in the catabolism of retinoic acid, have been developed as RAMBAs. Liarozole and rambazole, have been studied in the treatment of ARCI(29–31,42). A large-scale multi-center Phase II/III trial in LI evaluated oral liarozole (75 mg and 150 mg once daily) given during 12 weeks compared to placebo and showed that liarozole (0.1 g/day is now used) is an effective treatment for ichthyosis with results that are at least comparable to those of acitretin(30). Liarozole 5% cream is effective in ARCI and treatment is general well tolerated. Administration of liarozole 5% cream can elevated plasma concentrations in patients with ARCI.(31) Orphan

drug status have been granted for liarozole in both Europe and the US but Liarozole development has now been discontinued.

Systemic Retinoids During Childhood—Systemic retinoids are occasionally used in childhood and in the newborn period. Perhaps the most important neonatal usage is for harlequin ichthyosis (HI). HI is characterized by an "armor" of thick scale plates separated by deep fissures, ectropion, and eclabium. The nose and ears are flattened and appear rudimentary. Constricting bands can surround the extremities and these neonates are more prone to sepsis, dehydration, and impaired thermoregulation. Babies who survive into infancy and beyond develop skin changes resembling severe CIE.(43) Two recent studies have reported 83%–86% of patients with HI treated with an oral retinoid survived(44;45). Among the survivors, treatment was started within the first 7 days of life in 80% and 70% received 1 course of treatment, 20% had 2 separate courses(44). In contrast, 76% of babies who did not received retinoids died and 63% died by day 3. Some of these differences may be related to availability of high quality neonatal intensive care and by socioeconomic factors, and we are aware of HI infants who have survived without the use of retinoids. Controlled clinical trials would clarify the true contribution of retinoid administration to HI survival.

In HI, topical or systemic retinoids are most useful in combating soft-tissue constrictions that lead to functional impairment. If distal digits become necrotic because of constricting scale, retinoids help relieve those constrictions. It has been postulated that thoracic constriction by thick scale can impede breathing and can be reduced by retinoid therapy. Most patients with HI reported in the literature have been treated with acitretin(43, 45);.liquid acitretin is not widely available, however, and may take several days to obtain, thereby delaying treatment. The retinoid dose usually ranged from 0.5 to 2.5 mg/kg, but has been adjusted according to response, tolerability and severity of ichthyosis. Improvement in hyperkeratosis, ectropion, and eclabium, pliability of the skin, limb movements, sucking, and eyelid closing have been noted within a week of starting therapy(46). The duration of therapy is variable, and long-term therapy may be required. Treatment has been continued for several years in some patients, and it may be required indefinitely to prevent relapse(44). To minimize long-term toxic effects, it is recommended that the retinoid dose be as low as possible, close to 0.5 mg/kg/d.(44, 47) Symptoms suggestive of skeletal toxicity should be promptly investigated, particularly in those children receiving doses greater than 1.0 mg/kg/d.(45, 47). However, the severity of skin involvement after birth is usually much less severe than that at birth, and if there is improvement, long-term use may not be indicated.

Epidermolytic Ichthyosis

Epidermolytic ichthyosis (EI, formerly called epidermolytic hyperkeratosis) is an autosomal dominant disorder with the distinctive histopathology of vacuolar degeneration of the epidermis (epidermal lysis) and associated hyperkeratosis.(48) The disorder is due to mutations in the genes that encode either keratin 1 or 10.(49) Vörner described an epidermolytic ichthyosis involving only the palms and soles which is due to mutations in the gene encoding keratin 9, a keratin expressed only in volar surfaces. Six clinical phenotypes of EI have been described with variable scaling manifestations and extent of involvement(50). Subtypes with more extensive involvement benefit more from retinoids than those with mild or limited involvement. Patients who have thick, hystrix, spiny hyperkeratotic skin are prone to tearing of the fragile epidermis secondary to traction. Reducing the thick hyperkeratosis through keratolytics and systemic retinoids can greatly improve skin appearance and function (Figure 2a,b). Because of the fragility of the epidermis, bacterial colonization and infection is common in EI and treatment with antibiotics is frequently necessary. By reduction in the hyperkeratosis, systemic retinoid

therapy can reduce the frequency of skin infection. EI skin tends to be fragile and to blister, and this tendency can be exaggerated by retinoids, particularly on volar skin. Therefore, it is particularly important in treating EI to start initially at a low dose and increase slowly to avoid exacerbating the tendency to blister(7) and to discontinue the retinoids intermittently as fragility ensues.

Pityriasis Rubra Pilaris

Pityriasis Rubra Pilaris (PRP) is an uncommon (1:5,000–1:50,000) inflammatory papulosquamous disorder of unknown cause(51, 52). It affects both children and adults, but is found more commonly in adults. It affects males and females equally. Retinoids, alone or in combination with other therapies, are a mainstay of treatment for PRP.

Most PRP cases are acquired. However, when the disease is inherited, autosomal dominant, autosomal recessive, and X-linked patterns have been reported.(53) Griffiths proposed that PRP be classified into five subtypes, based on age of onset, morphologic presentation and chronicity (Table 1)(51). The most common and best characterized variant, Type 1 (Classical Adult), is characterized by erythematous plaques, often starting on the scalp and spreading cephalocaudally, follicular keratotic papules, and thick “carnuba wax” palmoplantar keratoderma. Ectropion is a common complication. Uninvolved areas, or “islands of sparing”, are characteristic of the disease. These islands of sparing can aid clinical differentiation from psoriasis, especially if erythroderma develops.

Nail changes are much less common in PRP than in psoriasis. Hair and teeth abnormalities are rare, except in the Type II (Atypical Adult), which sometimes can present with alopecia. More recently, a sixth subtype associated with HIV infection has been identified.(54, 55) This variant is often follicular-based and pustular. For a summary of clinical characteristics in the six subtypes, see Table I.

Retinoids in PRP—Before synthetic retinoids were developed, high doses of vitamin A were reported to improve PRP, even though blood levels of vitamin A often were normal in these patients(3). Once synthetic retinoids became available, treatment with isotretinoin, 40 mg twice daily, or acitretin 0.75 mg/kg/day were reported to control the skin lesions in adult onset classic PRP (Type 1). Retinoid treatment also has been combined with UVA or UVB, or with concurrent immunosuppressive or antiproliferative treatments such as methotrexate (5–30 mg/wk), azothioprine (50–200 mg/wk) or fumaric acid(52). UV treatment should be started slowly, as some patients with PRP are photosensitive. These agents may be effective by decreasing the keratinocyte hyperproliferation found in PRP(56). Potential side effects of retinoids, including elevations of cholesterol and triglycerides, skin dryness or stickiness, and pseudotumor cerebri must be balanced against their benefits, particularly in children.

Darier Disease and Hailey-Hailey Disease

Darier Disease (DD) and Hailey-Hailey Disease (HHD) are considered disorders of cornification or keratinization, based on their clinical presentations, histologic characteristics and impaired differentiation. More recently, the causative mutations in these diseases have been identified as defects in intracellular Ca^{2+} ATPases (ATP2A2 encoding protein SERCA2 in DD; ATP2C1 encoding SPCA1 in HHD). These Ca^{2+} ATPpases localize to the endoplasmic reticulum (ER) in DD or to the Golgi in HHD. Thus, while the relationship between the molecular abnormality and mechanism of retinoid action is not clear, retinoids are clinically efficacious, particularly in DD.

Clinical Characteristics—Both DD and HHD are uncommon diseases inherited as autosomal dominant. DD and HHD differ in their clinical morphology, localization and

histology. DD manifests as keratotic hyperpigmented papules that coalesce into plaques. These plaques generally are found in a seborrheic distribution (face, scalp, neck, shoulders, and central chest), although they eventually can involve most of the body surface, and, as the condition becomes more chronic, may form vegetating growths with a foul odor. Mosaic variants of DD often show a unilateral or patterned presentation. Plaques often present with a greasy appearing, grayish scale. The palms and soles can be affected with punctate keratoses that coalesce into generalized thickening. Nails often are involved with subungual hyperkeratosis, with alternating red and white streaks, longitudinal splitting and triangular "V-shaped" nicks of the distal edges. Mucosal surfaces such as the oropharynx and anorectal mucosae can also be involved.

HHD is characterized by chronic and recurrent erythematous patches, which may become bullous or vesicular, and develop into weeping, macerated, superinfected plaques. HHD generally presents in the flexural areas of the neck, groin, and axillae. Lesions in the genital area may become papular.

Both DD and HHD demonstrate loss of cellular attachments, particularly desmosomes, leading to the histologic pattern of acantholysis. DD additionally demonstrates apoptosis of keratinocytes. DD also is associated with neuropsychiatric disorders.(57)

DD patients also are at risk for eczema herpeticum(58) and eczema vaccinatum(59), and are not administered smallpox vaccine. Lithium can worsen DD(60, 61), perhaps because it suppresses SERCA2b protein expression(62).

Retinoid Actions in DD and HH—Retinoids commonly are used to treat DD, but less commonly are used to treat HHD. Retinoids may be useful in treating DD because they generally enhance keratinocyte differentiation(63), which is defective in both DD and HHD. However, retinoid treatment is a double-edged sword, as they also disrupt desmosome and adherens junction formation(64, 65). UV light downregulates expression of both ATP2A2 and ATP2C1 mRNA, perhaps explaining why both diseases are worsened by sunlight(66, 67). Retinoids have been shown to preserve both ATP2A2 and ATP2C1 expression after UV light exposure(66, 67).

Clinical Uses—Localized DD should first be treated with topical retinoids(68–70), although keratotic papules have been reported to appear at the periphery of treated areas. Oral retinoids are usually required to treat more generalized disease, starting at relatively low doses (eg. 0.5 mg/kg isotretinoin)(71) and adjusting upward until an effective dose is reached. Both etretinate and its active metabolite acitretin, starting at 10–25 mg/day and gradually increasing to approximately 0.6 mg/kg/day of acitretin, have been used to treat DD. There may be a difference in responsiveness of DD to different retinoid drugs. Patients whose DD was responsive to etretinate have been reported to be unresponsive to acitretin. (72) However other studies have found similar efficacy(73). Low doses of oral retinoids (etretinate or acitretin 25mg/day) also have been reported to improve HHD(74, 75), although most authors agree that retinoids are less effective in HHD than in DD, and recommend other therapeutic approaches(76, 77).

Adjuvant and Alternative Treatments—Topical 5-fluorouracil (5-FU) has been reported to reduce the keratotic papules in localized DD. Caution should be used to avoid excessive irritation of treated areas(78). Systemic antibiotic treatment is useful in both DD and HHD, particularly when directed against *Staphylococcus aureus*. Immunosuppression, either with topical corticosteroids or with systemic corticosteroids(79) or cyclosporin(80), also has been reported to improve the inflammatory component of these diseases. Ablative therapies such as laser (81–83), dermabrasion(84), or excision and grafting(85) may be used

in severe cases. Treatment with botulinum toxin(86) has been helpful in treating some HHD lesions, as it impairs sweating in injected areas.

Erythrokeratodermia Variabilis

The erythrokeratodermias are a group of skin disorders marked by localized patches of erythema and areas of either localized or generalized hyperkeratosis. In erythrokeratodermia varibilis patients develop persistent, hyperkeratotic plaques with accentuated skin markings. These may be generalized or localized. Sharply demarcated red patches develop which vary in size and may extend to several centimeters. The red areas are geographic in shape and move over minutes to hours. Some patients complain of burning in the areas of red patches. If left untreated, in some patients the plaques can lead to thick areas of hyperkeratosis.

The condition is usually inherited in an autosomal dominant pattern, but recessively inherited forms have been described. While involvement in most families is confined to the skin, a type of erythrokeratodermia with ataxia has been described. Mutations in *GJB3* (connexin 31) or *GJB4* (connexin 30.3) have been found which encode connexin proteins(87, 88). Connexins form gap junctions which permit intercellular signaling necessary for tissue homeostasis, growth control, development and synchronization of cellular response to stimuli(89).

Systemic retinoids are extremely effective, even at low doses, at dramatically improving the hyperkeratosis and in many patients minimizing the disease-associated red plaques(90, 91). Untreated patients with thick areas of hyperkeratosis should be started with low doses of isotretinoin or acitretin (≤0.25mg/kg/day) to avoid a sudden shedding of thick areas, a situation that can be uncomfortable. The dose can be increased as tolerated to achieve sufficient clearing. The efficacy of a very low dose of retinoid in this condition may be associated with less chronic toxicity (e.g., bone toxicity) and should be considered in the risk/benefit discussion when deciding to treat with systemic retinoids.

Keratitis-Ichthyosis–Deafness Syndrome

Skin involvement in KID syndrome varies from discrete red plaques to mild, generalized hyperkeratosis. Distinctive plaques may have a figurate appearance, sharp border and verrucous surface and may be symmetrically arrayed on the face. In contrast to the typical ichthyosiform scaling, patients may have thickened plaques with little scale. Patients may have an increased susceptibility to bacterial, fungal or viral infections. Scalp and nails may be affected. Infections of the hair-bearing areas of the scalp may lead to recurrent pustules, nodules and draining sinuses.

While patients have been reported to respond to acitretin treatment(92), the skin manifestations of KID syndrome are often not responsive to retinoids (93, 94). In addition, there has been concern that systemic retinoids can exacerbate the corneal neovasularization(95). Most cases of KID syndrome have been inherited in an autosomal dominant pattern and mutations in *GJB2* (encoding connexin 26) or *GJB6* (encoding connexin 30) have been found(96, 97). The reason that retinoids are very effective at low dose in the connexin disorder erythrokeratodermia variabilis, but not in the connexin disorder KID syndrome, is not understood.

Palmoplantar Keratodermas (PPKs)

Systemic retinoids have beneficial effects in some, but not all patients with PPK. Thinning of thick palmar skin can result in better movement of the digits, improved tactile sensation and enhanced function. Systemic retinoids can particularly benefit individuals with PPK who have constriction of digits (pseudo-ainhum) and are at risk for autoamputation (Fig 3a,

b). However, the effectiveness of acetretin in pachyonychia congenita has been poor(98), with many patients discontinuing retinoids due to increased pain, and 53% refusing to use oral retinoids again. Increased vulnerability and sensitivity during retinoid treatment may restrict normal function of hands and feet(99–101). This is particularly evident in epidermolytic ichthyosis affecting the palms and soles, in which blistering may occur with retinoid therapy. For PPK, lower doses of acitretin (10–25 mg/day) and treatment for a longer duration is generally superior to shorter duration, higher dosages and use of isotretinoin(98). Careful dose titration is warranted and patients should be fully informed about potential adverse effects and actively involved in the choice of treatment, dose and duration. Randomized, controlled, prospective clinical trials with both objective and patient-centered subjective endpoints are warranted to further define the PPK subsets that most benefit from retinoids.

Miscellaneous Disorders of Cornification

There are many individuals with ichthyosis who do not have a firm diagnosis. This may be because their disease is very rare or because the disorder is difficult to characterize. Since the systemic retinoids benefit many different ichthyosiform conditions, regardless of the underlying pathophysiology, a trial of retinoid therapy can be considered when hyperkeratosis and thickening become symptomatic and poorly responsive to topical agents.

SUMMARY

While systemic retinoid therapy has been known since the early Egyptians, its recent history has provided a major advance in the therapy of the ichthyoses and related skin types. For individual patients, care should be used in crafting an analysis of the risk/benefit ratio and in deciding when it is appropriate to start therapy. Since responses to retinoids are variable, many patients need a brief retinoid trial to assess benefit in order to make an informed risk/benefit decision.

Patients should understand that these drugs have side effects that can be severe, but are manageable. Effective topical therapies should be used continuously. Doses of retinoid should be kept as low as is practical. Monitoring laboratory parameters, particularly lipid and transaminase levels, consistent pregnancy avoidance, and for chronic therapy recurring evaluation of bone health, can insure that systemic retinoids are used safely and effectively.

Acknowledgments

This research was supported in part by the Intramural Research Program of the NCI, NIH, Medical Research Fund Tirol (MFF71, MFF153), the Austrian Science Fund (FWF J1901-MED, J2112-MED, P16990-B05), the European Cooperation in Science and Technology (COST Action BM0903)”

Reference List

1. Wolbach SB, Howe PR. TISSUE CHANGES FOLLOWING DEPRIVATION OF FAT-SOLUBLE A VITAMIN. J Exp Med. 1925 Nov 30; 42(6):753–77. [PubMed: 19869087]
2. Fujimaki Y. Formation of gastric carcinoma in albino rats fed on deficient diets. J Cancer Res. 1926; 10:469–77.
3. Griffiths WA. Vitamin A and pityriasis rubra pilaris. J Am Acad Dermatol. 1982 Oct.7(4):555. [PubMed: 7142464]
4. Frazier CN, Hu C. Cutaneous lesions associated with a deficiency in vitamin A in man. Arch Intern Med. 1931; 48(3):507–14.
5. Loewenthal LJA. A new manifestation in the syndrome of vitamin A deficiency. Arch Derm Syphilol. 1933; 28(5):700–8.

6. Peck SM, Chargin L, Sobotka H. Keratosis follicularis (Darier's disease) A vitamin A deficiency disease. Arch Derm Syphilol. 1941; 43(2):223–9.
7. Digiovanna JJ, Robinson-Bostom L. Ichthyosis: etiology, diagnosis, and management. Am J Clin Dermatol. 2003; 4(2):81–95. [PubMed: 12553849]
8. Digiovanna JJ, Zech LA, Ruddel ME, Gantt G, Peck GL. Etretinate. Persistent serum levels after long-term therapy. Arch Dermatol. 1989 Feb; 125(2):246–51. [PubMed: 2913962]
9. Lebwohl M, Drake L, Menter A, Koo J, Gottlieb AB, Zanolli M, Young M, McClelland P. Consensus conference: acitretin in combination with UVB or PUVA in the treatment of psoriasis. J Am Acad Dermatol. 2001 Oct; 45(4):544–53. [PubMed: 11568745]
10. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. Br J Dermatol. 2006 Feb; 154(2):267–76. [PubMed: 16433796]
11. Macbeth AE, Johnston GA. Twenty-one years of oral retinoid therapy in siblings with nonbullous ichthyosiform erythroderma. Clin Exp Dermatol. 2008 Mar; 33(2):190–1. [PubMed: 17927786]
12. Nassif PW, Nakandakari S, Fogagnolo L, Contin LA, Alves CJ. Epidermolytic hyperkeratosis: a follow-up of 23 years of use of systemic retinoids. An Bras Dermatol. 2011 Jul; 86(4 Suppl 1):S72–S75. [PubMed: 22068776]
13. Digiovanna JJ. Isotretinoin effects on bone. J Am Acad Dermatol. 2001 Nov; 45(5):S176–S182. [PubMed: 11606950]
14. Bastien J, Rochette-Egly C. Nuclear retinoid receptors and the transcription of retinoid-target genes. Gene. 2004:328.
15. Schug TT, Berry DC, Shaw NS, Travis SN, Noy N. Opposing effects of retinoic acid on cell growth result from alternate activation of two different nuclear receptors. Cell. 2007; 129(4)
16. Fisher C, Blumenberg M, Tomic-Canic M. Retinoid receptors and keratinocytes. Crit Rev Oral Biol Med. 1995; 6(4)
17. Asselineau D, Bernard BA, Bailly C, Darmon M. Retinoic acid improves epidermal morphogenesis. Dev Biol. 1989; 133(2)
18. Fritsch PO, Pohlin G, Langle U, Elias PM. Response of epidermal cell proliferation to orally administered aromatic retinoid. J Invest Dermatol. 1981; 77(3)
19. Fisher GJ, Voorhees JJ. Molecular mechanisms of retinoid actions in skin. FASEB J. 1996; 10(9)
20. Gerritsen MJ, van Pelt JP, van de Kerkhof PC. Response of the clinically uninvolved skin of psoriatic patients to tape stripping during acitretin treatment. Acta Derm Venereol. 1996; 76(1)
21. Griffiths CE, Elder JT, Bernard BA, Rossio P, Cromie MA, Finkel LJ, Shroot B, Voorhees JJ. Comparison of CD271 (adapalene) and all-trans retinoic acid in human skin: dissociation of epidermal effects and CRABP-II mRNA expression. J Invest Dermatol. 1993; 101(3)
22. Niwa S, Ochi T, Hirano Y, Wang T, Inagaki N, Shudo K, Nagai H. Effect of Am-80, a retinoid derivative, on 2, 4-dinitrofluorobenzene-induced contact dermatitis in mice. Pharmacology. 2000; 60(4)
23. Yoshioka A, Miyachi Y, Imamura S, Niwa Y. Anti-oxidant effects of retinoids on inflammatory skin diseases. Arch Dermatol Res. 1986; 278(3)
24. Blomhoff R, Green MH, Berg T, Norum KR. Transport and storage of vitamin A. Science. 1990; 250(4979)
25. Gao JG, Shih A, Gruber R, Schmuth M, Simon M. GS2 as a retinol transacylase and as a catalytic dyad independent regulator of retinylester accretion. Mol Genet Metab. 2009; 96(4)
26. Kurlandsky SB, Duell EA, Kang S, Voorhees JJ, Fisher GJ. Auto-regulation of retinoic acid biosynthesis through regulation of retinol esterification in human keratinocytes. J Biol Chem. 1996; 271(26)
27. Pavez LE, Chamcheu JC, Vahlquist A, Torma H. Both all-trans retinoic acid and cytochrome P450 (CYP26) inhibitors affect the expression of vitamin A metabolizing enzymes and retinoid biomarkers in organotypic epidermis. Arch Dermatol Res. 2009 Aug; 301(7):475–85. [PubMed: 19294396]
28. Fisher GJ, Esmann J, Griffiths CE, Talwar HS, Duell EA, Hammerberg C, Elder JT, Finkel LJ, Karabin GD, Nickoloff BJ. Cellular, immunologic and biochemical characterization of topical

retinoic acid-treated human skin. J Invest Dermatol. 1991 May; 96(5):699–707. [PubMed: 1673698]

29. Lucker GP, Heremans AM, Boegheim PJ, van deKerkhof PC, Steijlen PM. Oral treatment of ichthyosis by the cytochrome P-450 inhibitor liarozole. Br J Dermatol. 1997 Jan; 136(1):71–5. [PubMed: 9039298]
30. Verfaille CJ, Vanhoutte FP, Blanchet-Bardon C, van Steensel MA, Steijlen PM. Oral liarozole vs. acitretin in the treatment of ichthyosis: a phase II/III multicentre, double-blind, randomized, active-controlled study. Br J Dermatol. 2007 May; 156(5):965–73. [PubMed: 17263800]
31. Lucker GP, Verfaille CJ, Heremans AM, Vanhoutte FP, Boegheim JP, Steijlen PP. Topical liarozole in ichthyosis: a double-blind, left-right comparative study followed by a long-term open maintenance study. Br J Dermatol. 2005 Mar; 152(3):566–9. [PubMed: 15787831]
32. Bale, SJ.; Richard, G. Autosomal Recessive Congenital Ichthyosis. In: Pagon, RA.; Bird, TD.; Dolan, CR.; Stephens, K., editors. GeneReviews. University of Washington; Nov 19. 2009 Ref Type: Edited Book
33. Fischer J. Autosomal recessive congenital ichthyosis. J Invest Dermatol. 2009 Jun; 129(6):1319–21. [PubMed: 19434086]
34. Grall A, Guaguere E, Planchais S, Grond S, Bourrat E, Hausser I, Hitte C, Le GM, Derbois C, Kim GJ, Lagoutte L, Degorce-Rubiales F, Radner FP, Thomas A, Kury S, Bensignor E, Fontaine J, Pin D, Zimmermann R, Zechner R, Lathrop M, Galibert F, Andre C, Fischer J. PNPLA1 mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. Nat Genet. 2012; 44(2):140–7. [PubMed: 22246504]
35. Israeli S, Khamaysi Z, Fuchs-Telem D, Nousbeck J, Bergman R, Sarig O, Sprecher E. A mutation in LIPN, encoding epidermal lipase N, causes a late-onset form of autosomal-recessive congenital ichthyosis. Am J Hum Genet. 2011 Apr 8; 88(4):482–7. [PubMed: 21439540]
36. Blanchet-Bardon C, Nazzaro V, Rognin C, Geiger JM, Puissant A. Acitretin in the treatment of severe disorders of keratinization. Results of an open study. J Am Acad Dermatol. 1991 Jun; 24(6 Pt 1):982–6. [PubMed: 1831211]
37. Digiovanna, JJ. Retinoid treatment of the disorders of cornification. In: Vahlquist, A.; Duvic, M., editors. Retinoids and carotenoids in dermatology. New York: Informa Healthcare Inc; 2007. p. 153-69.
38. Kullavanijaya P, Kulthanan K. Clinical efficacy and side effects of acitretin on the disorders of keratinization: a one-year study. J Dermatol. 1993 Aug; 20(8):501–6. [PubMed: 8245313]
39. Lacour M, Mehta-Nikhar B, Atherton DJ, Harper JI. An appraisal of acitretin therapy in children with inherited disorders of keratinization. Br J Dermatol. 1996 Jun; 134(6):1023–9. [PubMed: 8763418]
40. Peck, GL.; Gross, EG.; Butkus, D. Comparative analysis of two retinoids in the treatment of disorders of keratinization. In: Orfanos, CE., editor. Retinoids: advances in basic research and therapy. New York: Springer Verlag; 1981. p. 279-86.
41. Steijlen PM, Van Dooren-Greebe RJ, van de Kerkhof PC. Acitretin in the treatment of lamellar ichthyosis. Br J Dermatol. 1994 Feb; 130(2):211–4. [PubMed: 8123574]
42. van Steensel MA. Emerging drugs for ichthyosis. Expert Opin Emerg Drugs. 2007 Nov; 12(4): 647–56. [PubMed: 17979605]
43. Haftek M, Cambazard F, Dhouailly D, Reano A, Simon M, Lachaux A, Serre G, Claudy A, Schmitt D. A longitudinal study of a harlequin infant presenting clinically as non-bullous congenital ichthyosiform erythroderma. Br J Dermatol. 1996 Sep; 135(3):448–53. [PubMed: 8949442]
44. Rajpopat S, Moss C, Mellerio J, Vahlquist A, Ganemo A, Hellstrom-Pigg M, Ilchyshyn A, Burrows N, Lestringant G, Taylor A, Kennedy C, Paige D, Harper J, Glover M, Fleckman P, Everman D, Fouani M, Kayserili H, Purvis D, Hobson E, Chu C, Mein C, Kelsell D, O'Toole E. Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. Arch Dermatol. 2011 Jun; 147(6):681–6. [PubMed: 21339420]
45. Singh S, Bhura M, Maheshwari A, Kumar A, Singh CP, Pandey SS. Successful treatment of harlequin ichthyosis with acitretin. Int J Dermatol. 2001 Jul; 40(7):472–3. [PubMed: 11679007]

46. Brecher AR, Orlow SJ. Oral retinoid therapy for dermatologic conditions in children and adolescents. J Am Acad Dermatol. 2003 Aug; 49(2):171–82. [PubMed: 12894062]
47. Digiovanna JJ, Peck GL. Oral synthetic retinoid treatment in children. Pediatr Dermatol. 1983 Jul; 1(1):77–88. [PubMed: 6238291]
48. Ross R, Digiovanna JJ, Capaldi L, Argenyi Z, Fleckman P, Robinson-Bostom L. Histopathologic characterization of epidermolytic hyperkeratosis: a systematic review of histology from the National Registry for Ichthyosis and Related Skin Disorders. J Am Acad Dermatol. 2008 Jul; 59(1):86–90. [PubMed: 18571597]
49. Digiovanna JJ, Bale SJ. Clinical heterogeneity in epidermolytic hyperkeratosis. Arch Dermatol. 1994 Aug; 130(8):1026–35. [PubMed: 8053700]
50. Oji V, Tadini G, Akiyama M, Blanchet BC, Bodemer C, Bourrat E, Coudiere P, Digiovanna JJ, Elias P, Fischer J, Fleckman P, Gina M, Harper J, Hashimoto T, Hausser I, Hennies HC, Hohl D, Hovnanian A, Ishida-Yamamoto A, Jacyk WK, Leachman S, Leigh I, Mazereeuw-Hautier J, Milstone L, Morice-Picard F, et al. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Soreze 2009. J Am Acad Dermatol. 2010 Oct; 63(4):607–41. [PubMed: 20643494]
51. Griffiths WA. Pityriasis rubra pilaris. Clin Exp Dermatol. 1980 Mar; 5(1):105–12. [PubMed: 7398119]
52. Sehgal VN, Jain MK, Mathur RP. Pityriasis rubra pilaris in Indians. Br J Dermatol. 1989 Dec; 121(6):821–2. [PubMed: 2611132]
53. Vasher M, Smithberger E, Lien MH, Fenske NA. Familial pityriasis rubra pilaris: report of a family and therapeutic response to etanercept. J Drugs Dermatol. 2010 Jul; 9(7):844–50. [PubMed: 20677542]
54. Blauvelt A, Nahass GT, Pardo RJ, Kerdel FA. Pityriasis rubra pilaris and HIV infection. J Am Acad Dermatol. 1991 May; 24(5 Pt 1):703–5. [PubMed: 1869640]
55. Misery I, Faure M, Claidy A. Pityriasis rubra pilaris and human immunodeficiency virus infection--type 6 pityriasis rubra pilaris? Br J Dermatol. 1996 Dec; 135(6):1008–9. [PubMed: 8983330]
56. Kanitakis J, Hoyo E, Chouvet B, Thivolet J, Faure M, Claudy A. Keratinocyte proliferation in epidermal keratinocyte disorders evaluated through PCNA/cyclin immunolabelling and AgNOR counting. Acta Derm Venereol. 1993 Oct; 73(5):370–5. [PubMed: 7904405]
57. Gordon-Smith K, Jones LA, Burge SM, Munro CS, Tavadia S, Craddock N. The neuropsychiatric phenotype in Darier disease. Br J Dermatol. 2010 Sep; 163(3):515–22. [PubMed: 20456342]
58. Kandasamy R, Hecker M, Choi M, Pile J. Darier disease complicated by disseminated zoster. Dermatol Online J. 2009; 15(2):6. [PubMed: 19336023]
59. Haase O, Moser A, Rose C, Kurth A, Zillikens D, Schmidt E. Generalized cowpox infection in a patient with Darier disease. Br J Dermatol. 2011 May; 164(5):1116–8. [PubMed: 21275935]
60. Milton GP, Peck GL, Fu JJ, Digiovanna JJ, Nordlund JJ, Thomas JH, Sanders SF. Exacerbation of Darier's disease by lithium carbonate. J Am Acad Dermatol. 1990 Nov; 23(5 Pt 1):926–8. [PubMed: 2123895]
61. Ngo J, Haber R. Exacerbation of Darier disease by lithium carbonate. J Cutan Med Surg. 2010 Mar; 14(2):80–4. [PubMed: 20338123]
62. Sule N, Teszas A, Kalman E, Szigeti R, Miseta A, Kellermayer R. Lithium suppresses epidermal SERCA2 and PMR1 levels in the rat. Pathol Oncol Res. 2006; 12(4):234–6. [PubMed: 17189987]
63. Kopan R, Traska G, Fuchs E. Retinoids as important regulators of terminal differentiation: examining keratin expression in individual epidermal cells at various stages of keratinization. J Cell Biol. 1987 Jul; 105(1):427–40. [PubMed: 2440897]
64. Humphries JD, Parry EJ, Watson RE, Garrod DR, Griffiths CE. All-trans retinoic acid compromises desmosome expression in human epidermis. Br J Dermatol. 1998 Oct; 139(4):577–84. [PubMed: 9892899]
65. Wanner R, Wolff B, Glowacki F, Kolde G, Wittig B. The loss of desmosomes after retinoic acid treatment results in an apparent inhibition of HaCaT keratinocyte differentiation. Arch Dermatol Res. 1999 Jun; 291(6):346–53. [PubMed: 10421061]

66. Mayuzumi N, Ikeda S, Kawada H, Ogawa H. Effects of drugs and anticytokine antibodies on expression of ATP2A2 and ATP2C1 in cultured normal human keratinocytes. Br J Dermatol. 2005 May; 152(5):920–4. [PubMed: 15888147]

67. Mayuzumi N, Ikeda S, Kawada H, Fan PS, Ogawa H. Effects of ultraviolet B irradiation, proinflammatory cytokines and raised extracellular calcium concentration on the expression of ATP2A2 and ATP2C1. Br J Dermatol. 2005 Apr; 152(4):697–701. [PubMed: 15840101]

68. Abe M, Inoue C, Yokoyama Y, Ishikawa O. Successful treatment of Darier's disease with adapalene gel. Pediatr Dermatol. 2011 Mar; 28(2):197–8. [PubMed: 20403120]

69. Burkhart CG, Burkhart CN. Tazarotene gel for Darier's disease. J Am Acad Dermatol. 1998 Jun; 38(6 Pt 1):1001–2. [PubMed: 9632016]

70. Casals M, Campoy A, Aspiolea F, Carrasco MA, Camps A. Successful treatment of linear Darier's disease with topical adapalene. J Eur Acad Dermatol Venereol. 2009 Feb; 23(2):237–8. [PubMed: 18624851]

71. Dicken CH, Bauer EA, Hazen PG, Krueger GG, Marks JG Jr, McGuire JS, Schachner LA. Isotretinoin treatment of Darier's disease. J Am Acad Dermatol. 1982 Apr; 6(4 Pt 2 Suppl):721–6. [PubMed: 7040515]

72. Bleiker TO, Bourke JF, Graham-Brown RA, Hutchinson PE. Etretinate may work where acitretin fails. Br J Dermatol. 1997 Mar; 136(3):368–70. [PubMed: 9115918]

73. Christophersen J, Geiger JM, Danneskiold-Samsoe P, Kragballe K, Larsen FG, Laurberg G, Serup J, Thomsen K. A double-blind comparison of acitretin and etretinate in the treatment of Darier's disease. Acta Derm Venereol. 1992; 72(2):150–2. [PubMed: 1350407]

74. Berger EM, Galadari HI, Gottlieb AB. Successful treatment of Hailey-Hailey disease with acitretin. J Drugs Dermatol. 2007 Jul; 6(7):734–6. [PubMed: 17763599]

75. Hunt MJ, Salisbury EL, Painter DM, Lee S. Vesiculobullous Hailey-Hailey disease: successful treatment with oral retinoids. Australas J Dermatol. 1996 Nov; 37(4):196–8. [PubMed: 8961587]

76. Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. Br J Dermatol. 1992 Mar; 126(3):275–82. [PubMed: 1554604]

77. Burge SM, Wilkinson JD. Darier-White disease: a review of the clinical features in 163 patients. J Am Acad Dermatol. 1992 Jul; 27(1):40–50. [PubMed: 1619075]

78. Schmidt H, Ochsendorf FR, Wolter M, Geisslinger G, Ludwig RJ, Kaufmann R. Topical 5-fluorouracil in Darier disease. Br J Dermatol. 2008 Jun; 158(6):1393–6. [PubMed: 18410420]

79. Speight EL. Vesiculobullous Darier's disease responsive to oral prednisolone. Br J Dermatol. 1998 Nov; 139(5):934–5. [PubMed: 9893210]

80. Shahidullah H, Humphreys F, Beveridge GW. Darier's disease: severe eczematization successfully treated with cyclosporin. Br J Dermatol. 1994 Nov; 131(5):713–6. [PubMed: 7999607]

81. Beier C, Kaufmann R. Efficacy of erbium:YAG laser ablation in Darier disease and Hailey-Hailey disease. Arch Dermatol. 1999 Apr; 135(4):423–7. [PubMed: 10206049]

82. Katz TM, Firoz BF, Goldberg LH, Friedman PM. Treatment of Darier's disease using a 1,550-nm erbium-doped fiber laser. Dermatol Surg. 2010; 36(1):142–6. [PubMed: 19912279]

83. McElroy JA, Mehregan DA, Roenigk RK. Carbon dioxide laser vaporization of recalcitrant symptomatic plaques of Hailey-Hailey disease and Darier's disease. J Am Acad Dermatol. 1990 Nov; 23(5 Pt 1):893–7. [PubMed: 2123894]

84. Zachariae H. Dermabrasion of Hailey-Hailey disease and Darier's disease. J Am Acad Dermatol. 1992 Jul.27(1):136. [PubMed: 1619066]

85. Cooper SM, Burge SM. Darier's disease: epidemiology, pathophysiology, and management. Am J Clin Dermatol. 2003; 4(2):97–105. [PubMed: 12553850]

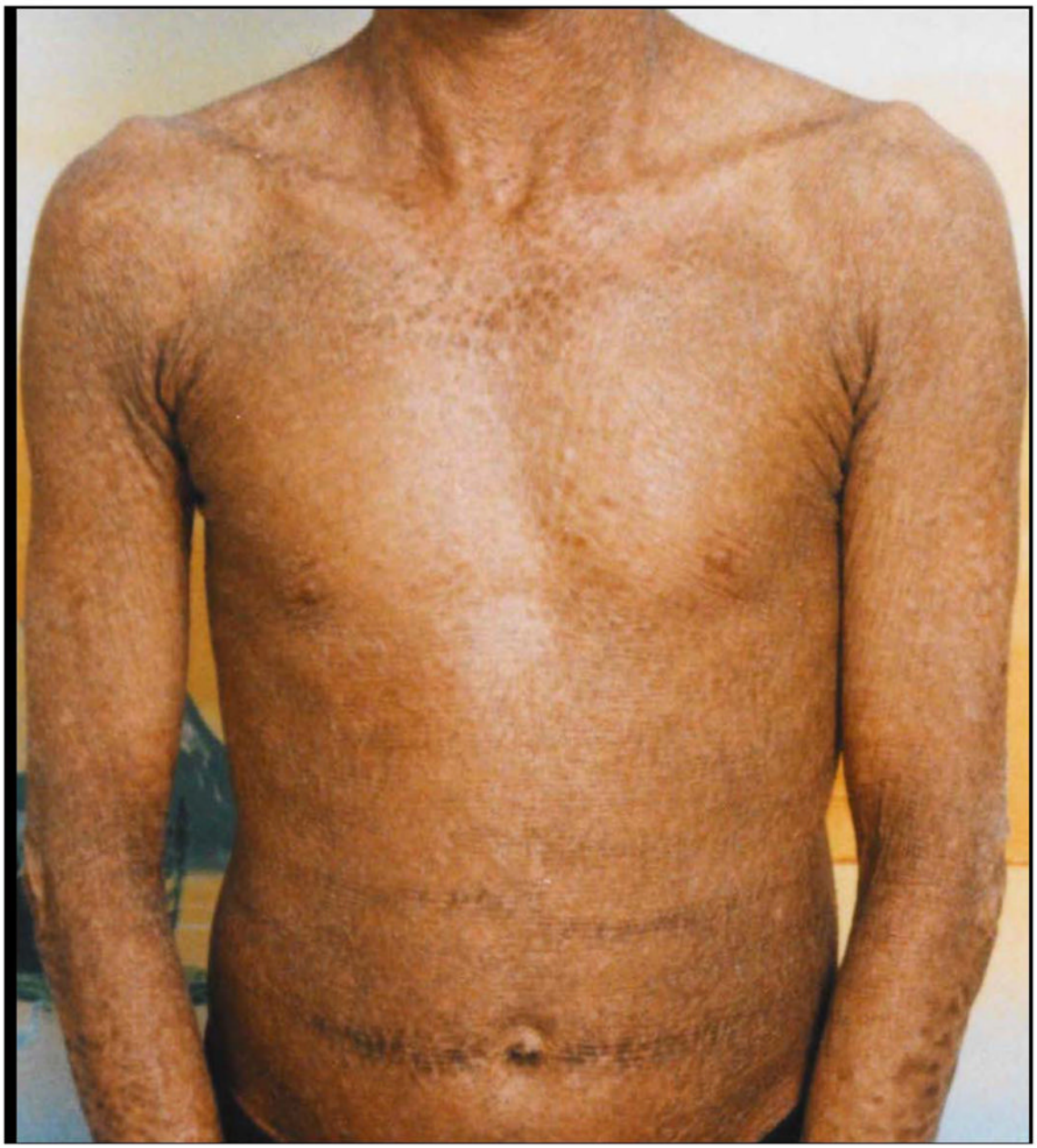
86. Lapiere JC, Hirsh A, Gordon KB, Cook B, Montalvo A. Botulinum toxin type A for the treatment of axillary Hailey-Hailey disease. Dermatol Surg. 2000 Apr; 26(4):371–4. [PubMed: 10759827]

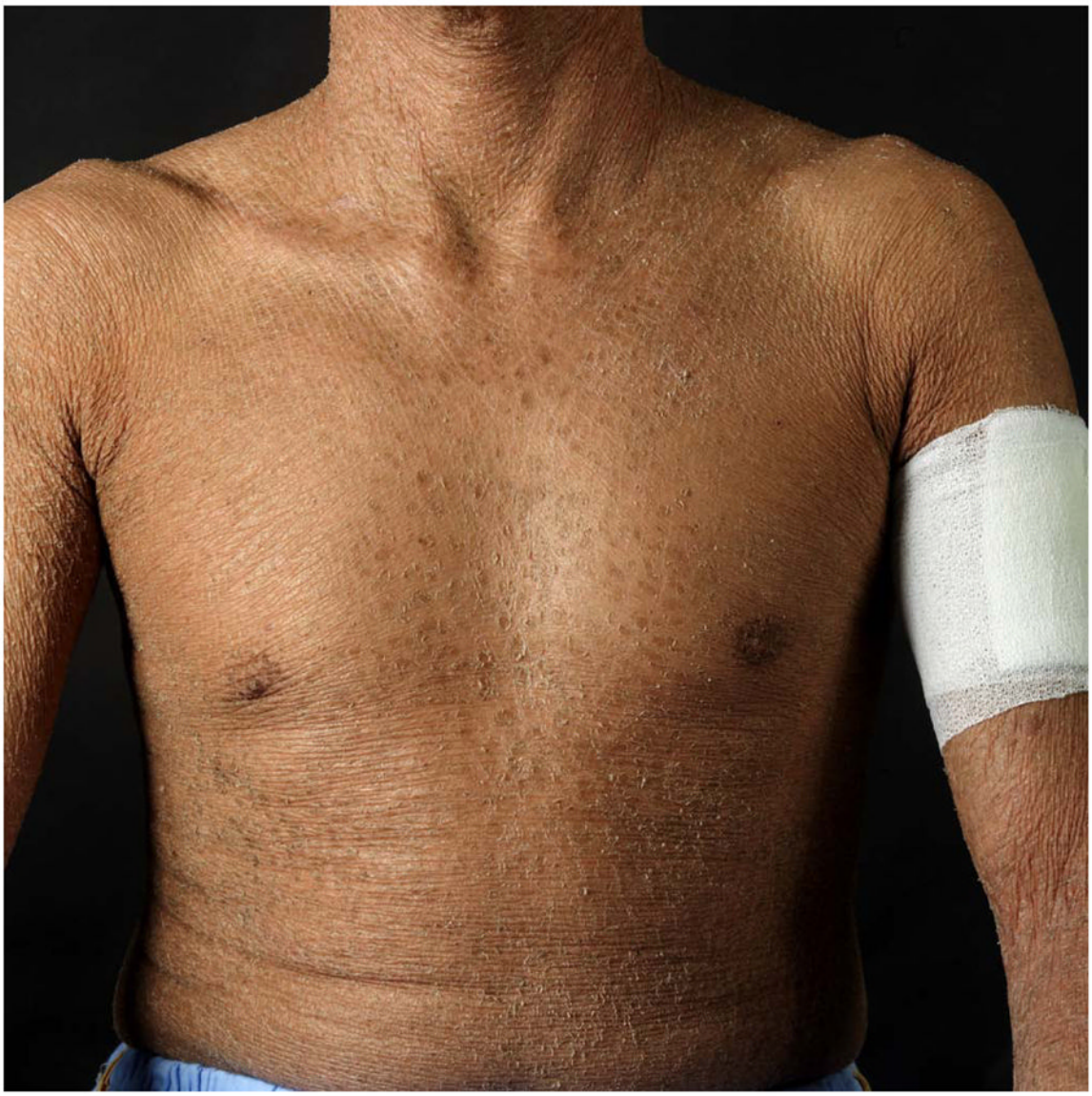
87. Richard G, Smith LE, Bailey RA, Itin P, Hohl D, Epstein EH Jr, Digiovanna JJ, Compton JG, Bale SJ. Mutations in the human connexin gene GJB3 cause erythrokeratodermia variabilis. Nat Genet. 1998 Dec; 20(4):366–9. [PubMed: 9843209]

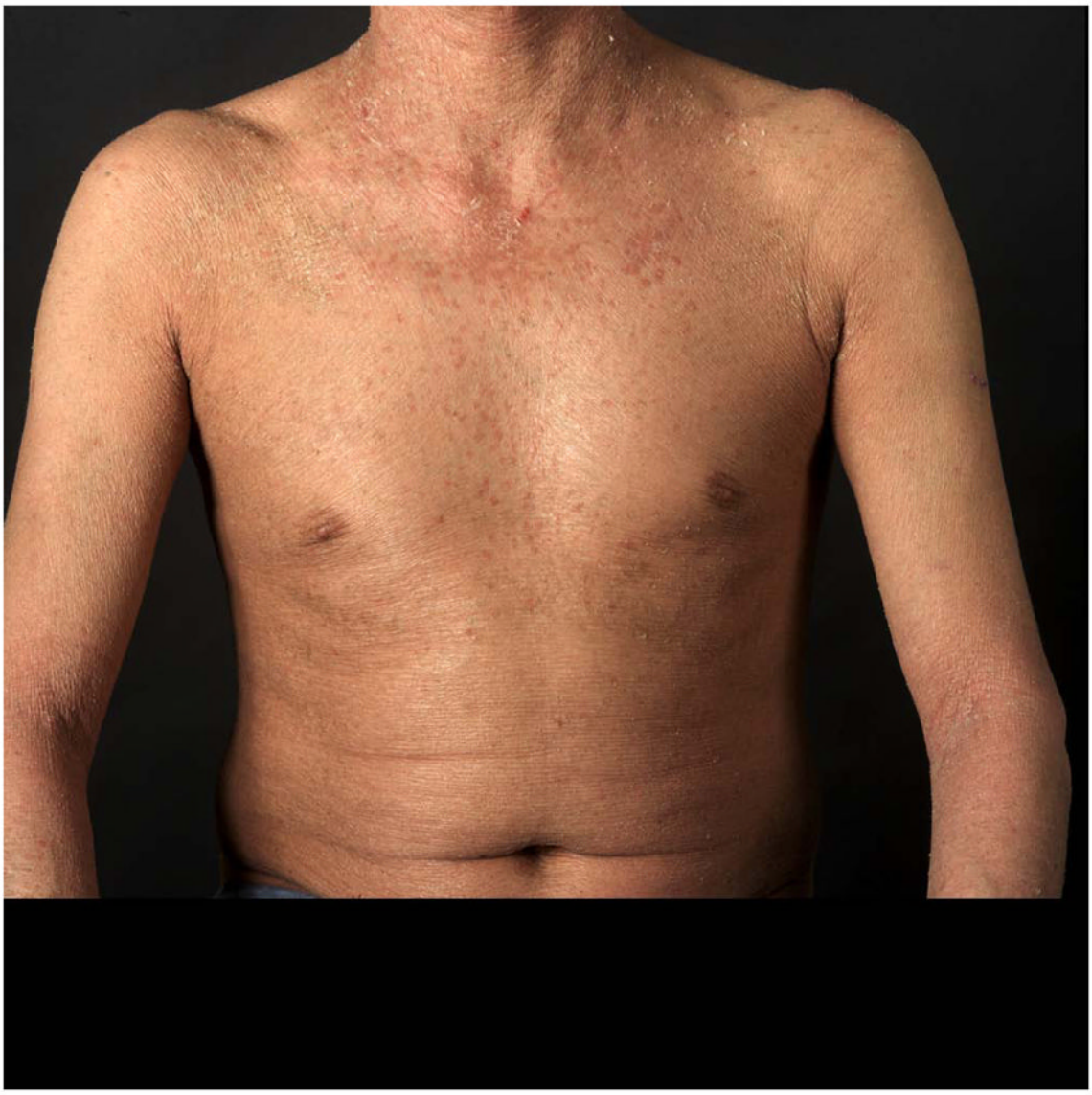
88. Richard G, Brown N, Rouan F, Van der Schroeff JG, Bijlsma E, Eichenfield LF, Sybert VP, Greer KE, Hogan P, Campanelli C, Compton JG, Bale SJ, Digiovanna JJ, Uitto J. Genetic heterogeneity

in erythrokeratodermia variabilis: novel mutations in the connexin gene GJB4 (Cx30.3) and genotype-phenotype correlations. J Invest Dermatol. 2003 Apr; 120(4):601–9. [PubMed: 12648223]

89. Richard G. Connexins: a connection with the skin. Exp Dermatol. 2000 Apr; 9(2):77–96. [PubMed: 10772382]
90. Rappaport IP, Goldes JA, Goltz RW. Erythrokeratodermia variabilis treated with isotretinoin. A clinical, histologic, and ultrastructural study. Arch Dermatol. 1986 Apr; 122(4):441–5. [PubMed: 2420287]
91. Singh N, Thappa DM. Erythrokeratoderma variabilis responding to low-dose isotretinoin. Pediatr Dermatol. 2010 Jan; 27(1):111–3. [PubMed: 20199434]
92. Sahoo B, Handa S, Kaur I, Radotra BD, Kumar B. KID syndrome: response to acitretin. J Dermatol. 2002 Aug; 29(8):499–502. [PubMed: 12227483]
93. Langer K, Konrad K, Wolff K. Keratitis, ichthyosis and deafness (KID)-syndrome: report of three cases and a review of the literature. Br J Dermatol. 1990 May; 122(5):689–97. [PubMed: 2191710]
94. Maintz L, Betz RC, Allam JP, Wenzel J, Jaksche A, Friedrichs N, Bieber T, Novak N. Keratitis-ichthyosis-deafness syndrome in association with follicular occlusion triad. Eur J Dermatol. 2005 Sep; 15(5):347–52. [PubMed: 16172043]
95. Hazen PG, Carney JM, Langston RH, Meisler DM. Corneal effect of isotretinoin: possible exacerbation of corneal neovascularization in a patient with the keratitis, ichthyosis, deafness ("KID") syndrome. J Am Acad Dermatol. 1986 Jan; 14(1):141–2. [PubMed: 2419373]
96. Jan AY, Amin S, Ratajczak P, Richard G, Sybert VP. Genetic heterogeneity of KID syndrome: identification of a Cx30 gene (GJB6) mutation in a patient with KID syndrome and congenital atrichia. J Invest Dermatol. 2004 May; 122(5):1108–13. [PubMed: 15140211]
97. Richard G, Rouan F, Willoughby CE, Brown N, Chung P, Ryynanen M, Jabs EW, Bale SJ, Digiovanna JJ, Uitto J, Russell L. Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. Am J Hum Genet. 2002 May; 70(5): 1341–8. [PubMed: 11912510]
98. Gruber R, Edlinger M, Kaspar RL, Hansen CD, Leachman S, Milstone LM, Smith FJ, Sidoroff A, Fritsch PO, Schmuth M. An appraisal of oral retinoids in the treatment of pachyonychia congenita. Journal of the American Academy of Dermatology. 2011
99. Baden HP, Bronstein BR, Rand RE. Hereditary callosities with blisters. Report of a family and review. J Am Acad Dermatol. 1984; 11(3)
100. Fritsch P, Honigsmann H, Jaschke E. Epidermolytic hereditary palmoplantar keratoderma. Report of a family and treatment with an oral aromatic retinoid. Br J Dermatol. 1978; 99(5)
101. Williams ML, Elias PM. Nature of skin fragility in patients receiving retinoids for systemic effect. Arch Dermatol. 1981; 117(10)







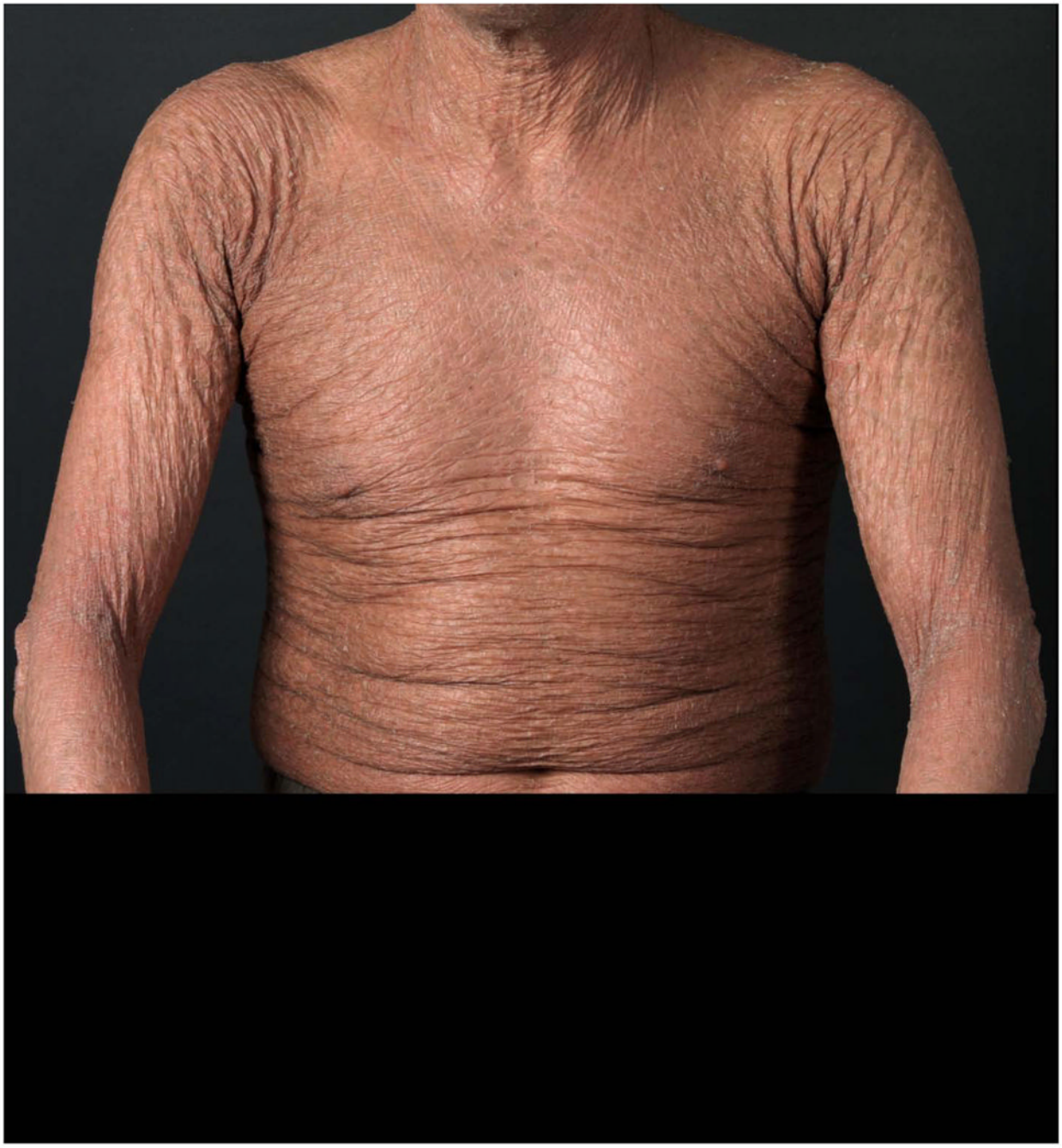


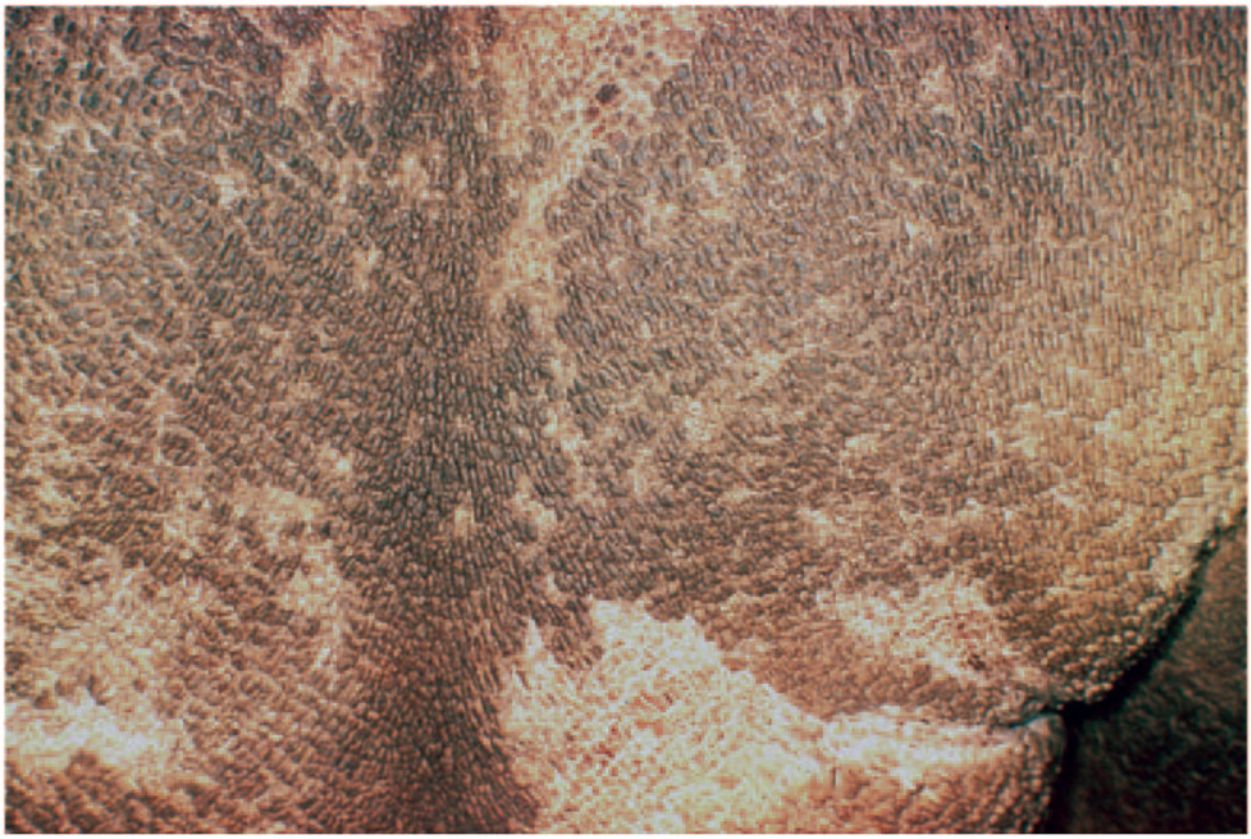
Figure 1.

Figure 1a. A patient with autosomal recessive congenital ichthyosis-lamellar ichthyosis type before treatment with oral retinoid therapy. (We are grateful to Dr. Robert Gruber for providing clinical images.)

Figure 1b. After 4 weeks of therapy with acitretin at 30 mg/day.

Figure 1c. After 8 weeks of therapy with acitretin at 30 mg/day.

Figure 1d. Twelve weeks after discontinuation of acitretin involvement with lamellar scale has returned.



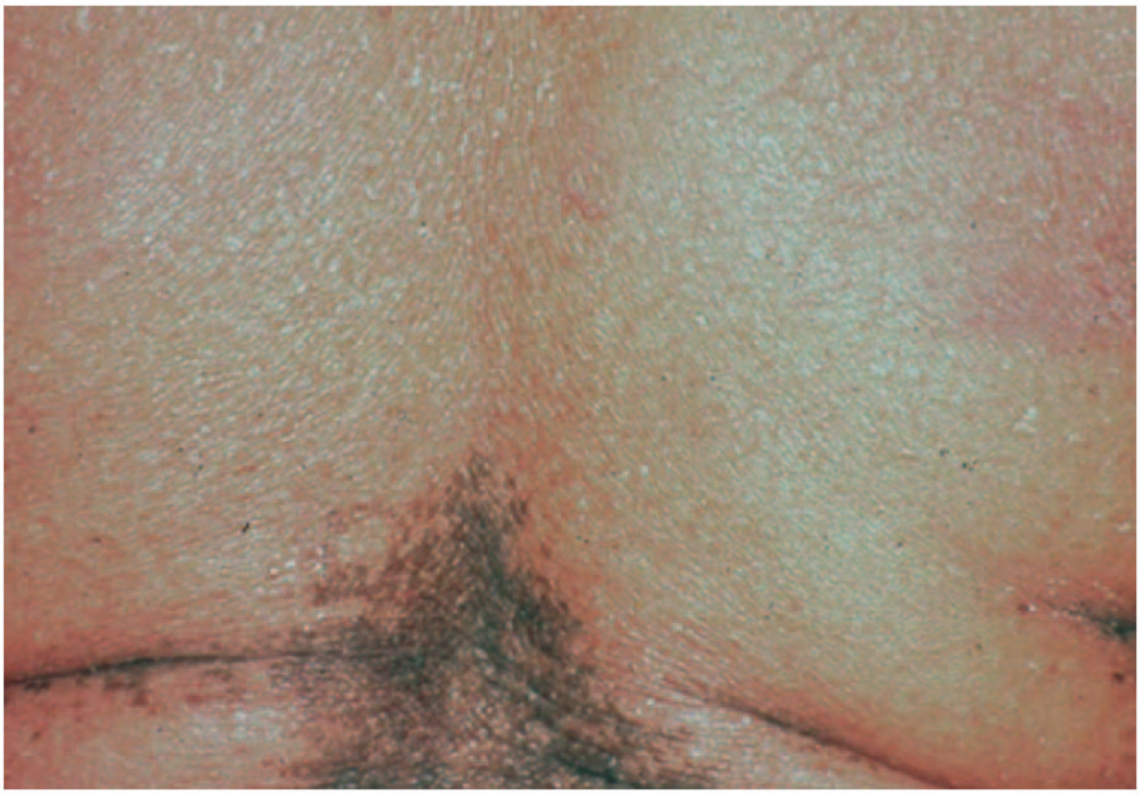
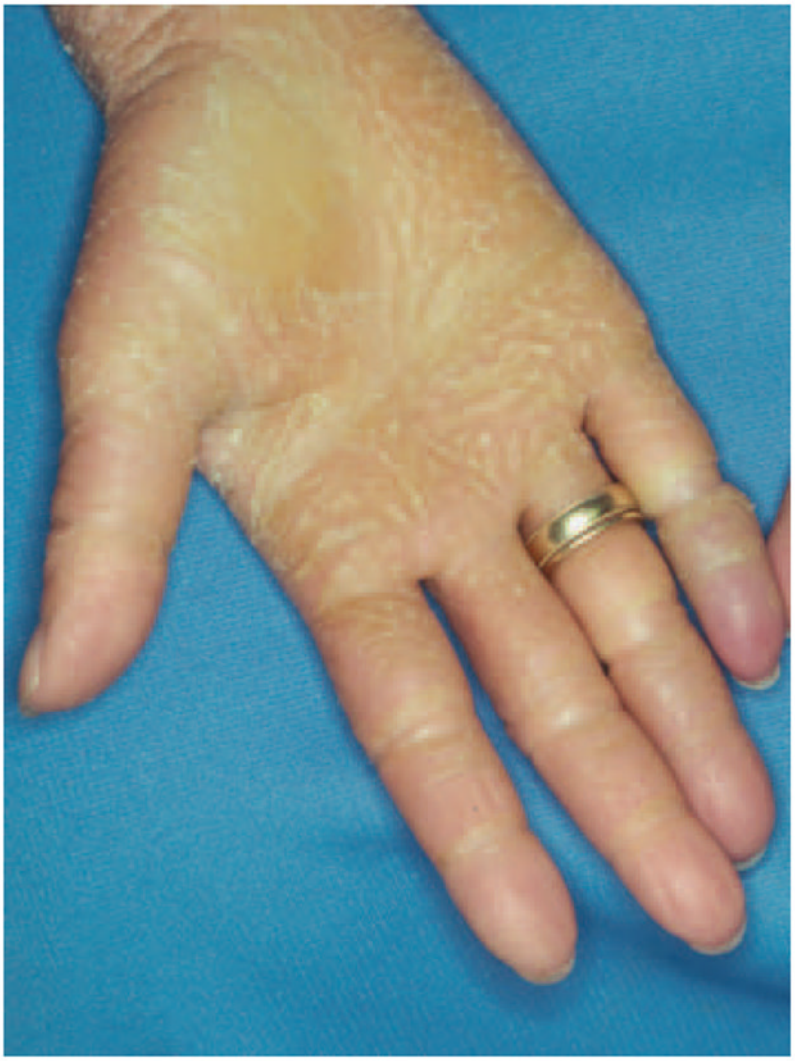


Figure 2.
Figure 2a. Epidermolytic ichthyosis (EI) of back before treatment with isotretinoin. Note thick, hystrix type of hyperkeratosis.
Figure 2b. EI of back on isotretinoin therapy. The thick hyperkeratosis has been shed and has left a more normal, pliable skin surface.



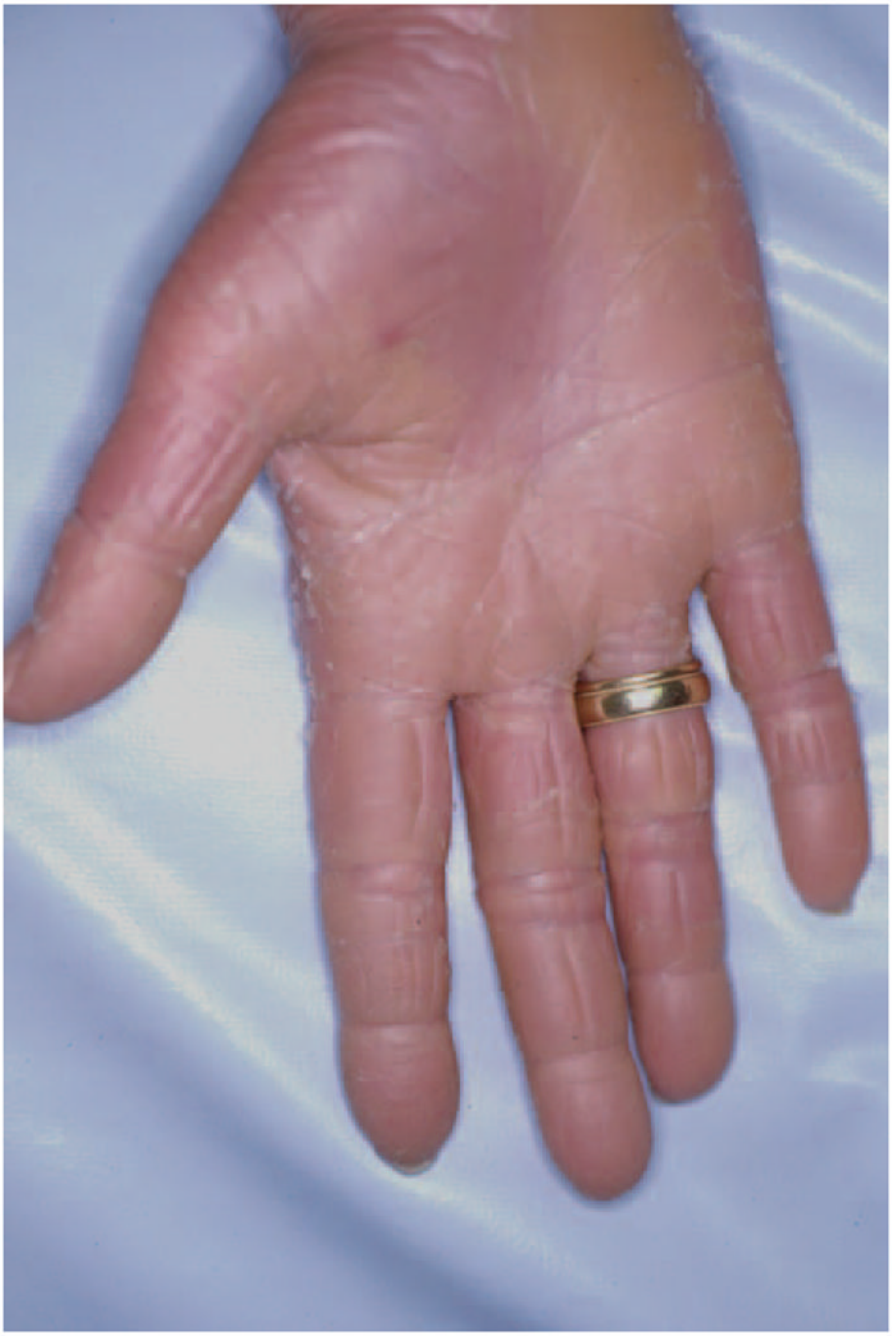


Figure 3.
Figure 3a. PPK with honeycomb appearance and pseudo-ainhum before acitretin.
Figure 3b. During treatment with acitretin, the pseudo-ainhum is improved.

Table 1

Summary of PRP Subtypes

Type	Name	Prevalence	Distribution	Prognosis	Associations
1.	Classical Adult	50–60%	Generalized	Median disease length Is 3 years	Rare association with malignancy
2.	Atypical Adult	5%	Generalized	20% remission in 3 years	Alopecia (uncommon)
3.	Classical Juvenile	10%	Generalized	Remits in 1–2 years	Can be temporally associated with bacterial or viral infections
4.	Circumscribed Juvenile	25%	Distal aspects of extremities	Unpredictable	See 3, above
5.	Atypical Juvenile	5%	Generalized	Does not remit	See 3, above
6.	HIV associated	Unknown	Face, chest and upper back	Does not remit	HIV