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INVITED ARTICLE

Systemic retinoids in the management of ichthyoses and related skin types

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ABSTRACT: The term retinoid includes both natural and synthetic derivatives of vitamin A. Retinoid-containing treatments have been used since ~1550BC by the early Egyptians. Treatment of ichthyosiform disorders with retinoids dates back at least to the 1930s. 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: acitretin, ectropion, ichthyosis, isotretinoin, retinoid

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Introduction

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 and Howe (1) and to cancer in 1926 by Fujimaki (2). Pityriasis rubra pilaris (PRP) 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 (DD), Peck, Chargin and Sobotka reasoned that the dyskeratosis of DD 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 article 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 objectives of treatment include hydration, lubrication, and removal of thick scales (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 (EI), 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 (RA)) 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 United States, 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 2 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. Acitretin often becomes undetectable after 3–4 weeks; however, it also has the potential for body storage and longer persistence. 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 with 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 (FDA)–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 DD and EI, 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 with 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. 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 women 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, RA receptors and retinoid X receptors (RXRs) that typically act as either hetero- or homodimers. 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. 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.

Retinoids were used to treat ichthyosis long before their actions on gene transcription were appreciated. Unfortunately, direct studies of how they work in ichthyosis are lacking. Retinoid actions on keratinocyte protein expression (17) predict that their effects will be complex and may be different in normal skin, diseased skin, and tissue culture models. Several retinoid effects surely have relevance to ichthyosis: they thin the stratum corneum (18,19), facilitate desquamation (20) through down-regulation of protein components of corneodesmosomes (17,21) and they have anti-inflammatory properties (22,23).

RA metabolism blocking agents (RAMBAs)

In addition to modulation by exogenous administration of RA, keratinocyte differentiation can be affected by alterations in the intracellular concentrations of RA (16). 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 RA) protein is a membrane receptor, mediating retinol uptake into cells. Cellular retinol binding proteins (CRBPs I and II) bind intracellular retinol. Intracellular retinoid concentrations are controlled by: (i) dehydrogenases involved in RA synthesis (RalDH2, RoDH-4), (ii) lecithin : retinol acyl transferase, acyl CoA : retinol acyl transferase, and GS2 (25–27), which mediate esterification with long-chain fatty acids, and (iii) CYP26, which degrades RA.

CYP26 inhibitors, also termed 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 FDA. RAMBAs are not currently approved in the United States.

Disease specific considerations

Ichthyoses

Autosomal-recessive congenital ichthyosis (ARCI). The clinical presentation and severity of 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 (PPK), 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. *ABCA12* is the major gene causing HI and has also been described in some LI patients. Mutations in *ALOXE3*, ALOX12*, NIPAL4 and PNPLA1* are present in CIE or intermediate LI/NCIE phenotypes (29–32).

Retinoids have been reported efficacious in the treatment of ARCI based on case reports and series (5–11,33–38). 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

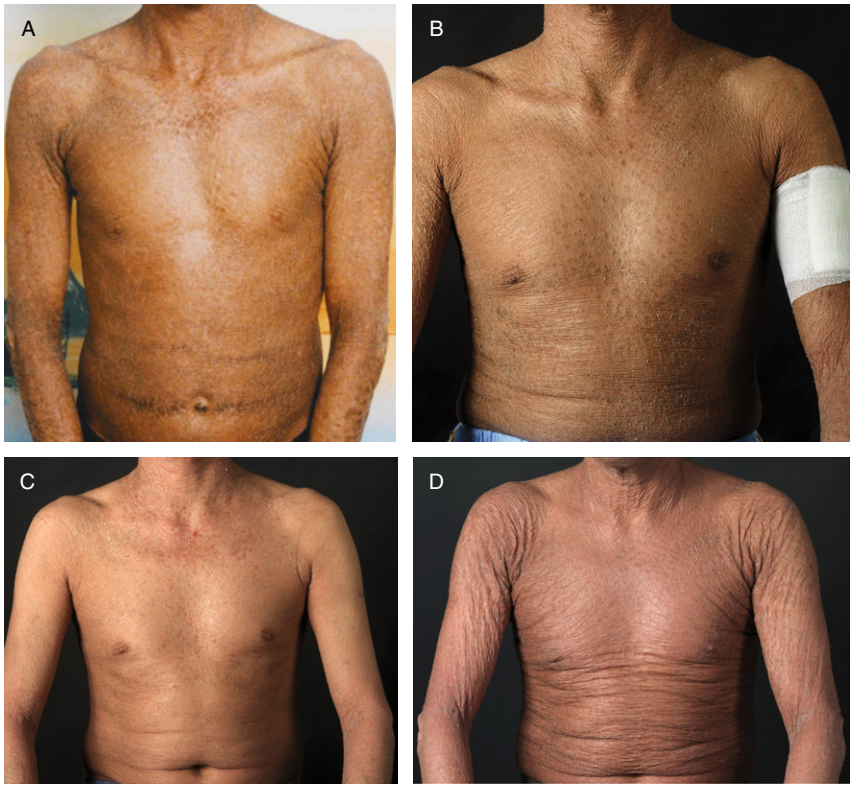

FIG. 1. **(A) A patient with autosomal-recessive congenital ichthyosis-lamellar ichthyosis type before treatment with oral retinoid therapy. (B) After 4 weeks of therapy with acitretin at 30 mg/day. (C) After 8 weeks of therapy with acitretin at 30 mg/day. (D) Twelve weeks after discontinuation of acitretin involvement with lamellar scale has returned.**

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 (38). 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 those 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) (38). Cosmetically acceptable hair re-growth has been described in a patient with severe alopecia after 4 years of oral retinoid therapy (38). 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 (34). 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 RA, have been developed as RAMBAs. Liarozole and rambazole, have been studied in the treatment of ARCI (39–42). A large-scale multicenter Phase II/III trial in LI evaluated oral liarozole (75 mg and 150 mg once daily) given during 12 weeks compared with placebo and showed that liarozole is an effective treatment for ichthyosis with results that are at least comparable to those of acitretin (40). Liarozole 5% cream is effective in ARCI and treatment was generally well tolerated. Administration of liarozole 5% cream can elevated plasma concentrations in patients with ARCI (41). Orphan drug status has 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 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 one course of treatment and 20% had two 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 the 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 scales 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); however, liquid acitretin is not widely available, 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/day (44,47). Symptoms suggestive of skeletal toxicity should be promptly investigated, particularly in those children receiving doses greater than 1.0 mg/kg/day (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 hyperkeratosis

Epidermolytic hyperkeratosis (EHK) is an autosomal-dominant disorder with the distinctive histopathology of vacuolar degeneration of the epidermis (epidermal lysis) and associated hyperkeratosis (48). The disorder is known to be due to mutations in the genes for either keratin 1 or 10 (49). Vörner described an epidermolytic ichthyosis involving only the palms and soles, which has been found to be due to mutations in the gene encoding keratin 9, a keratin expressed only in volar surfaces. The term epidermolytic ichthyosis has been suggested for ichthyoses characterized by epidermolysis and caused by keratin mutations (50). Six clinical phenotypes of EHK have been described with variations in character and extent of involvement. Subtypes with more extensive involvement have greater benefit 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 (Fig. 2a,b). Because of the fragility of the epidermis, bacterial colonization and infection is common in EHK and treatment with antibiotics is frequently necessary. By reduction in the hyperkeratosis, systemic retinoid therapy can reduce the frequency of skin infection. EHK 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 EHK to start initially at a low dose and increase slowly to avoid exacerbating the tendency to blister (7).

PRP

PRP is an uncommon (1 : 5000–1 : 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 men and women 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” PPK. 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.

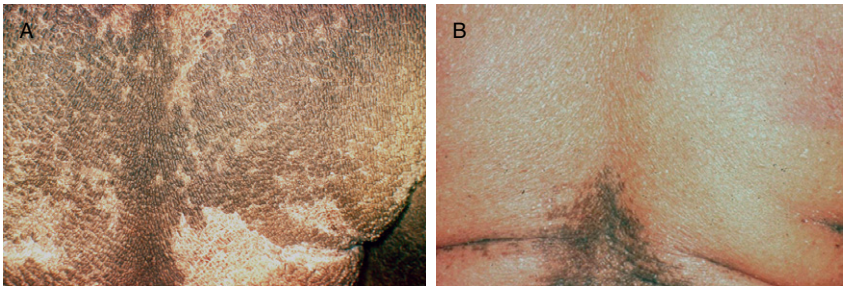

FIG. 2. **(A) Epidermolytic ichthyosis (EI) of back before treatment with isotretinoin. Note thick, hystrix type of hyperkeratosis. (B) EI of back on isotretinoin therapy. The thick hyperkeratosis has been shed and has left a more normal, pliable skin surface.**

Table 1. Summary of pityriasis rubra pilaris 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

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 1.

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 were often normal in these patients (3). Once synthetic retinoids became available, treatment with isotretinoin or acitretin were reported to control the skin lesions in adult onset classic PRP (Type 1). Retinoid treatment also has been combined with ultraviolet (UV) A or UVB, or with concurrent immunosuppressive or antiproliferative treatments such as methotrexate (5–30 mg/week), azothioprine (50–200 mg/week), 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.

DD and Hailey–Hailey disease (HHD)

DD and 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+} adenosine triphosphate (ATP) ases (*ATP2A2* encoding protein SERCA2 in DD; *ATP2C1* encoding SPCA1 in HHD). These Ca^{2+} ATPpases localize to the endoplasmic reticulum 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 is also associated with neuropsychiatric disorders (57).

DD patients are also 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 are less commonly 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 down-regulates 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 (e.g., 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 25 mg/day) have also 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 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), has also 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 that 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 ($\leq$0.25 mg/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, and deafness (KID) syndrome

Skin involvement in KID syndrome varies from discrete red plaques to mild, generalized hyperkerato-

sis. 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.

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 auto-amputation (Fig. 3a,b). However, the effectiveness of acetretin in pachyonychia congenita has been poor (98), with many patients discontinuing retinoids because of 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 EI 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 end points are warranted to further define the PPK subsets that most benefit from retinoids.

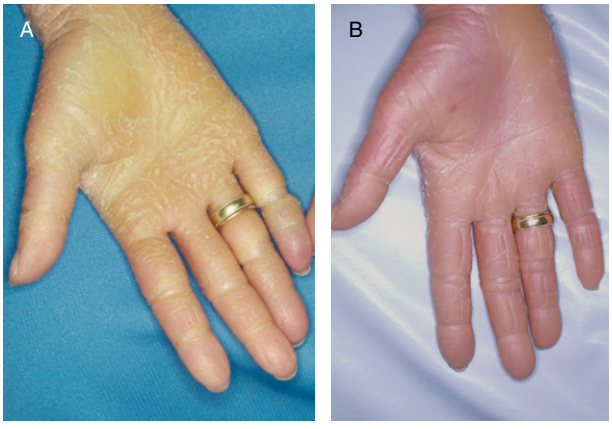

FIG. 3. (A) Palmoplantar keratoderma (PPK) with honeycomb appearance and pseudo-ainhum before acitretin. (B) During treatment with acitretin, the pseudo-ainhum is improved.

Miscellaneous disorders of cornification

There are many individuals with ichthyosis who do not have a firm diagnosis. This may be due to the fact that their disease is very rare or that the disorder is difficult to characterize. Because 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. Because 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.

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Since the preparation of this manuscript, mutations in CARD14 have been found in four families with autosomal dominant PRP (Am J Hum Genet. 2012 Jul 13;91(1):163–70. doi: 10.1016/j.ajhg.2012.05.010. Epub 2012 Jun 14. Familial pityriasis rubra pilaris is caused by mutations in CARD14. Fuchs-Telem D, Sarig O, van Steensel MA, Isakov O, Israeli S, Nousbeck J, Richard K, Winnepenninckx V, Vernooij M, Shomron N, Uitto J, Fleckman P, Richard G, Sprecher E.)

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