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A review of three systemic retinoids in dermatology: acitretin, isotretinoin and bexarotene

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Retinoids are synthetic and natural analogues of vitamin A that have various effects on cellular differentiation, cellular proliferation, immune system, and embryonic development. The present study reviews the history of systemic retinoids in medicine, the structure of synthetic retinoids and their mechanisms. The main focus is on their biologic functions, clinical uses, and the adverse effects of isotretinoin, acitretin, and bexarotene representing the most commonly used first, second, and third generation systemic retinoids, respectively.

Keywords: acitretin, bexarotene, etretinate, isotretinoin, retinoids

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INTRODUCTION

The term "retinoid" applies to the synthetic and natural analogues of vitamin A [1]. Retinoids show biologic activities that are specific to vitamin A. To enhance the beneficial effects of vitamin A, especially its anti-keratinization property and the promotion of cellular differentiation, new synthetic retinoids were engineered [2,3]. Generally, retinoids bind to specific nuclear receptors and consequently activate these receptors. However, these bindings are not an essential prerequisite for their functions. Binding to complex groups of intra nuclear receptors (retinoic acid receptors: RARs and retinoid X receptors: RXRs) is the cornerstone of understanding the basic mechanisms of retinoids [4]. Retinoids are involved in diverse biological activities including cellular growth, cellular cohesion, immunomodulatory effects, and anti-tumor functions [3]. The diversity of biologic effects of retinoids has led to various clinical applications of these drugs in dermatology and oncology [1].

The introduction of isotretinoin, etretinate, and its active metabolite acitretin and bexarotene, the RXR-selective retinoid, to dermatology has revolutionized medical therapy in dermatology [1,4].

HISTORY

In 1909, Step found that egg-yolk extract contained a vital substance. Soon afterwards, this substance, first named fat soluble A and then vitamin A, was also found in other natural resources such as milk cream and cod liver oil. The proper beta carotene formula was discovered by Karrer et al in 1931 [5]. In 1937, vitamin A was synthesized for the first time. In 1976, Michael Sporn and his colleagues used the term 'Retinoid' for the first time [4].

BASIC KNOWLEDGE ON RETINOIDS

Chemical structure

The biochemical structure of vitamin A (retinol) is composed of three major units: the cyclic end group (cyclic ring), the polyene side chain, and the polar end (Figure 1). Modifications in any of these three components results in the production of different synthetic retinoids [6]. The first generation of retinoids (non-aromatics) including tretinoin (all-trans-retinoic acid), isotretinoin and alitretinoin, are synthesized by chemical modification of the polar end and polyene side chain. Replacing the cyclic end group of vitamin A with substituted and non-substituted rings results in the formation of the second generation of retinoids (mono-aromatics) including etretinate and acitretin. The third generation of retinoids, also called arotinoids, is produced through the cyclization of the polyene side-chain [2,7]. This group includes bexarotene, tazarotene, and adapalene.

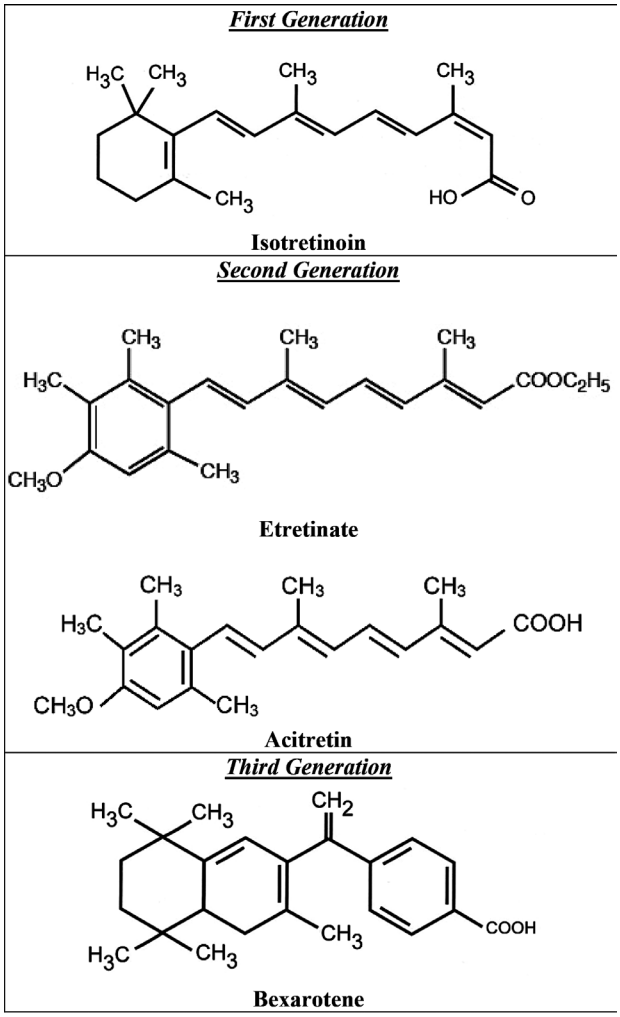

Figure 1. Chemical Structure of Retinoids

Therapeutic index of retinoids

The therapeutic index (TI) of retinoids is defined as the ratio of the lowest intraperitoneal dose per day causing hypervitaminosis A after 14 days, to the lowest intraperitoneal dose per week causing a regression of papillomas by 50% after 14 days [5,7]. For instance, the TI of tretinoin and isotretinoin is as follows:

Tretinoin (All-*trans* Retinoic Acid: ATRA) TI = 0.2

Isotretinoin TI = 0.5

From vitamin A to retinoic acid (vitamin A metabolism)

Vitamin A is not synthesized in the human body. Therefore, it should be supplied from dietary regiments [4]. Vitamin A is found in three inter-convertible forms; retinol (vitamin A alcohol) which is the main dietary, transport and storage form [3], retinal (vitamin A aldehyde) which is necessary for visual function [5], and retinoic acid (vitamin A acid) [3], which is the biologically active ligand that can bind to intracellular retinoid receptors [3]. Retinyl esters are hydrolyzed to retinol in the intestinal lumen. Next, it is absorbed and stored in the liver. Subsequently, retinol is converted to retinoic acid [3]. Retinoic acid is predominantly found in all-*trans* form (ATRA) and only a small fraction of it is isomerized into 13-cis retinoic [2].

Transport of retinoids

Retinoic acids are transported in blood stream by albumin. Two intracellular carriers named cytosolic retinoic acid binding protein1 and 2 (CRABP1, 2) transport retinoic acids into the nucleus. These carriers have important regulatory functions, as well. CRABP-1 regulates the levels of retinoic acid in different tissues and CRABP-2 is the main form in the human epidermis and mediates the morphogenic activity of vitamin A. In fact, CRABP-2 is an important mediator in epidermal differentiation; extremely high levels of CRABP-2 are found in the psoriatic skin (800% increase compared to normal skin) as well as in

other disorders of keratinization such as ichthyosis, Darier disease, pityriasis rubra pilaris and keratosis pilaris. It has been shown that treatment with retinoids reduces the expression of epidermal CRABP-2. Interestingly, higher levels of CRABP may be associated with increased sensitivity of the lesion to retinoids [2].

Retinoid receptors and mechanism of action

These receptors belong to the superfamily of ligand-activated nuclear receptors, including receptors of vitamin D, thyroid hormone, steroid and peroxisome proliferator activated receptor (PPAR) [8]. Two distinct families of retinoid receptors are found: retinoic acid receptor (RARs) and retinoic X receptors (RXRs). Each family has three isoforms encoded by different genes: alpha (α), beta (β) and gamma (γ). Retinoids have different receptor binding properties. ATRA binds only to RAR, while 9-cis-retinoic acid is the only known physiologic ligand for RXR. Bexarotene is an example of highly selective RXR-binding synthetic retinoids (rexinoids) [2,4,9]. Briefly, through three mechanisms, retinoid receptors modulate gene expression: first, transactivation via direct binding to retinoic acid–response elements (RARE)in target gene promoters; second, transrepression of activator protein 1 (AP-1) and other transcription factors; third, protein–protein interactions and competition with other nuclear receptors (Vitamin D Receptor, VDR) [4].

Pharmacokinetics of systemic retinoids

Metabolism

Generally, the bioavailability of oral retinoids is increased when administered with food, especially with fatty meals [2]. Systemic retinoids are transported in the blood stream by albumin, lipoproteins, or other plasma proteins and are mainly stored and metabolized in the liver [2]. Isotretinoin is oxidized to 4-oxo-isotretinoin which is quickly eliminated by the liver and the kidney [3]. In contrast to vitamin A, isotretinoin is not stored in the liver or adipose tissue [3]. Acitretin is metabolized through isomerization, forming cis-acitretin [2]. Bexarotene is metabolized by cytochrome P450 3A4 [3]. It is oxidized to 6- and 7-hydroxy-bexarotene and subsequently to 6- and 7-oxo-bexarotene [2].

Half-Lives

Teratogenicity is a major concern in the administration of systemic retinoids. Therefore, the length of the time these drugs are present in the body is crucial; terminal elimination half-lives of retinoids are 10 to 20 hours for isotretinoin, 50 hours for acitretin, 7 to 9 hours for bexarotene and as long as 80 to 160 days for etretinate [2].

Unlike isotretinoin and acitretin, etretinate is highly lipophilic, approximately 50 times more lipophilic than acitretin. Therefore, it can be stored in adipose tissues for several years. In fact, the serum level of etretinate is markedly decreased after the discontinuation of treatment. However, low levels of circulating etretinate may be detectable for up to 2.9 years after discontinuation of the drug [2]. The pharmacologic properties of isotretinoin, acitretin, etretinate and bexarotene are summarized in Table 1.

Acitretin re-esterification (reverse metabolism)

Oral alcohol intake promotes the re-esterification of acitretin to etretinate. In the human hepatocytes culture, this conversion only occurs in simultaneous presence of ethanol and acitretin. In a study on 10 psoriatic patients, the plasma level of etretinate reached 2.5-56.7 nanograms per milliliter (ng/ml) three months after their treatment with a daily acitretin dose of 30 mg.

In another study, the concentration of etretinate in subcutaneous fat tissues was 100 times greater

Table 1. Pharmacologic properties of systemic retinoids

Retinoid	Peak Level (hrs)	Bioavailability	Protein Binding	Half-life	Metabolism	Excretion
Isotretinoin	3	25%	Albumin 99%	10-20 (hrs)	Hepatic	Fecal, Renal
Etretinate	4	44%	Lipoprotein 99%	80-160 Days	Hepatic	Fecal, Renal
Acitretin	4	60%	Albumin 95%	50 (hrs)	Hepatic	Fecal, Renal
Bexarotene	2	Unknown	Plasma protein 99%	7 (hrs)	Hepatic	Hepatobiliary

than its plasma level after 4-11 months of treatment. However, the clinical relevance and importance of this finding in not clear. Theoretically, etretinate can be expelled from fat tissues in certain situations (e.g. accelerated fat catabolism in response to starvation or thermogenesis or in the presence of some lipophilic drugs). These observations led to the extension of the recommended therapeutic contraception period in female patients receiving acitretin up to 2 years by manufacturers and up to 3 years by Food and Drug Administration (FDA); similar to etretinate. Some authors have suggested measuring etretinate and acitretin levels in subcutaneous fat tissues even when they are undetectable in the plasma [2,10-12].

Biologic effect of retinoids

Retinoids regulate various biologic functions in the human body; they are involved in the regulation of cell proliferation and differentiation, exert anti-keratinization properties and alter cell cohesiveness. They also exhibit anti-acne and anti-seborrheic effects, have immunologic, anti-inflammatory and anti-proliferative functions and are also involved in the induction of apoptosis, tumor prevention, and affect extracellular matrix [3]. The important effects of retinoids on the immune system are discussed below in more detail.

McKerrow et al revealed that the activity of natural killer (NK) cells was significantly reduced in acne patients after 6 and 12 weeks of treatment with isotretinoin. This effect, however, was not observed in psoriasis; in fact, etretinate treatment resulted in increasing the number and activity of NK cells in these patients. The authors suggested that isotretinoin was the safer of the two retinoids for administration in transplant recipients, particularly in the immediate post-transplant period when NK cells are highly active [13].

Retinoic acid is the key regulator in transforming growth factor-beta (TGF-β) dependent immune responses. TGF-β converts naive T cells into regulatory T cells (Treg) that prevent autoimmunity and inflammation. Paradoxically, in the presence of interleukin (IL)-6, TGF-β promotes the differentiation of naive T lymphocytes into proinflammatory IL-17-producing T helper 17 cells (Th-17) which are involved in inflammation and autoimmunity. Retinoic acid inhibits the IL-6-induced conversion of naive T cells to proinflammatory Th-17 cells and promotes anti-inflammatory Treg differentiation; therefore, retinoids are physiologically involved in maintaining the TGF-β-induced immunologic balance [14].

Recent studies have revealed that the conversion of vitamin A to retinoic acid in intestinal dendritic cells promotes the differentiation of naive T-cells to Tregs, which are important suppressors of immune responses. Eventually, this process leads to the accumulation of Tregs in the intestines. Oral tolerance is known to be induced by local immune-suppressor cells, making the body immunologically unresponsive to certain antigens presented to intestinal mucosa. Therefore, retinoids may be involved in the induction of tolerance [15].

ACITRETIN IN CLINICAL DERMATOLOGY

Psoriasis

The therapeutic profile of acitretin in the treatment of psoriasis is similar to that of etretinate although the latter is no longer commercially available [3]. The response of plaque-type psoriasis to both drugs is variable with complete clearance in 30%, significant improvement in 50%, and treatment-failure in 20% of the treated patients and a 60-70% decrease in Psoriasis Area and Severity Index (PASI) score after 12 weeks of treatment [3]. Double blinded studies have proven the efficacy of higher doses of acitretin at 50-75 mg/day over placebo [16]. Acitretin is the FDA-approved drug for the treatment of psoriasis [17].

The results of treatment in generalized or palmoplantar pustular psoriasis are more impressive; four weeks after the treatment with acitretin, a five-time reduction was noted in the total number of pustular lesions in the patients with palmoplantar pustolosis [18]. In another study, a 10-time reduction in the number of pustular lesions was noted in the patients treated with either acitretin or etretinate [19].

In the treatment of psoriasis, combination therapies, including acitretin or etretinate with photochemotherapy, have been shown to be more effective than systemic retinoids alone. Four clinical trials have shown that retinoid PUVA (Re-PUVA) is associated with earlier and higher rates of response and lower cumulative radiation

exposure. Bath-PUVA with acitretin or etretinate is more effective than either of the two treatments given alone. A combination of acitretin and UVB has also been advocated. Re-UVB is more effective than acitretin or phototherapy alone [20,21].

Pityriasis rubra pilaris (PRP)

Anecdotally, acitretin (0.5 mg/kg/day) is considered the first-line treatment for PRP. In a retrospective study, 7 out of 9 patients showed complete or partial clearance after 18.8 months of treatment with acitretin or etretinate [22].

Ichthyoses and keratoderma

Acitretin has been used in the treatment of several types of ichthyoses; 29 children with ichthyosis including 9 lamellar ichthyosis, 5 non-bullous ichthyosiform erythroderma, 4 bullous ichthyosiform erythroderma, 3 Sjogren-Larsson Syndrome, and 8 other ichthyosiform diseases were treated with either etretinate or acitretin. Significant improvements were noted in all but 3 patients [23]. In another clinical trial, in patients with congenital ichthyosiform erythroderma, lamellar ichthyosis, and Papillon-Lefevre syndrome, the therapeutic responses to acitretin were better than the previously reported responses to etretinate [24]. Application of acitretin is not justified in mild keratinization disorders such as ichthyosis vulgaris and mild forms of X-linked recessive ichthyosis [16,25].

Darier's disease

The efficacy of acitretin and etretinate has been shown in different studies in patients with Darier's disease [26,27]. It is suggested to start with a dose of 10-25 mg/day followed by cautious gradual dose adjustments to reach an optimal therapeutic level [28].

Lichen planus

Acitretin (30 mg/day) is an effective treatment for patients with severe lichen planus; in a double-blind clinical trial of 60 patients with lichen planus, 64% of the patients showed significant improvements with acitretin vs. 13% of the patients who received placebo [29].

In a meta-analysis by Cribier et al [30], the authors suggested acitretin as the first-line treatment for cutaneous lichen planus. Moreover, acitretin may also be preferred in hyperkeratotic lichen planus due to its modulatory effect on keratinization [30].

Lichen sclerosis

In a multi-center clinical trial of women with vulvar lichen sclerosus, the use of acitretin (20-30mg/day) resulted in clinical response in 14 out of 22 patients vs. 6 out of 24 patients in the placebo group [31]. However, due to the high drop-out rate, the study had a high risk of bias [16].

Lupus erythematosus

Acitretin has been successfully used in chronic and subacute cutaneous Lupus erythematosus. In a clinical trial of 58 patients with cutaneous lupus, comparable clinical responses of 46% and 50% were noted in the patients treated with acitretin (50 mg/day) and hydroxyl chloroquine (400 mg/day), respectively. A higher incidence of adverse effects was observed in the acitretin group which resulted in discontinuing the treatment in four patients [32]. In an open trial, complete clearance or marked improvement was noted in 15 out of 20 patients with acitretin, which was superior to the previous treatment with antimalarics and ⁄or systemic steroids in seven patients [33].

Immunobullous disorders

Successful treatment of refractory lesions of pemphigus vegetans as a result of adding etretinate to systemic steroids has been reported [34].

Hailey-Hailey disease

Two cases of refractory Hailey-Hailey disease improved dramatically with a daily acitretin dose of 25 mg [35,36]. Recently, successful treatment with a combination of acitretin and cyclosporine has been reported [37].

Miscellaneous

Etretinate and acitretin have been also used with some success in other dermatologic diseases such as plasma cell vulvitis, Zoon's balanitis (as an

adjunctive treatment to circumcision) and lipoid proteinosis [38-40].

ISOTRETINOIN IN CLINICAL DERMATOLOGY

Acne vulgaris

The introduction of isotretinoin was a major advancement in the treatment of acne. Isotretinoin is a unique drug that has been shown to induce long-term remission of acne. This is because isotretinoin can inhibit almost all principal etiologic factors in the pathogenesis of acne; sebum production, inflammation (through in vivo inhibition of monocyte and neutrophil chemotaxis), comedogenesis and propionibacterium acnes proliferation [41,42]. Isotretinoin is the only retinoid that can suppress the production of sebum. The proliferation, differentiation, and activity of basal sebocytes are decreased by isotretinoin. In addition, isotretinoin induces the apoptosis of sebocyte [43].

In the United States of America, isotretinoin has been approved by FDA in severe recalcitrant nodular acne. With increasing experience, its use has been extended to patients with less severe forms of acne who are unresponsive to conventional treatments, especially in cases with scarring or significant psychological distress [43]. However, according to European directive for the systemic use of isotretinoin in acne, it should only be used in severe acne cases (nodular, conglobata) which are not responding to appropriate antibiotics and topical therapy. It is not recommended for children under 12 years of age. All types of chemical and physical peeling and wax depilation should be avoided during the therapeutic use of isotretinoin and six months after discontinuing the therapy [44].

Different treatment regimens exist regarding the optimal dosage of this drug. The typical prescription dosage is 0.5mg/kg daily (divided in two doses) with a therapeutic range of 0.5-1 mg/kg/day. One month after initiating the treatment, the starting dose should be adjusted based on the clinical response and tolerance. A total cumulative dose of 120-150mg/kg is usually required during the treatment period [43].

Isotretinoin is also indicated in hidradenitis suppurativa and dissecting cellulitis of the scalp as parts of the follicular occlusion tetrad; however, the effect of isotretinoin is limited, especially in the former [3].

Rosacea

In resistant papulopustular rosacea, isotretinoin is an alternative therapy. A daily dose of 10-60 mg has been advocated (a dose of 0.5-1 mg/kg/day) [45,46]. A period of 16-20 weeks is recommended for isotretinoin therapy [47]. Previous studies have shown the good effect of isotretinoin on papules and pustules. After one month of therapy, a significant reduction has been reported in the number of papules and pustules [46]. Isotretinoin also improves erythema; however, its effect on erythema is slow and incomplete [46].

In a randomized clinical trial, isotretinoin at a dose of 0.3 mg/kg/day was the most effective dose for papulopustular and phymatous rosacea [48]. Long-term or continuous low dose of isotretinoin (10-20 mg/day and sometimes as low as 20 mg weekly) has been proposed for treatment of chronic and recalcitrant rosacea [49].

Due to the impairment of meibomian function and ocular dryness, isotretinoin is not recommended for use in ocular rosacea [45].

Psoriasis

The efficacy of isotretinoin (1.5-2 mg/kg) on pustular and plaque type psoriasis has been shown in some studies; however, its effect is inferior to that of etretinate or acitretin [50,51]. Some authors prefer isotretinoin in women of childbearing age with pustular psoriasis, due to the shorter duration of teratogenicity [52]. A good response of childhood pustular psoriasis to isotretinoin has also been reported [53]. A combination of isotretinoin plus PUVA has been used with good results [54-56]. Acitretin plus narrow band UVB (NBUVB) has a therapeutic effect similar to that of acitretin-PUVA [21]. We showed that a combination of isotretinoin (0.5-1mg/kg) plus NBUVB could reduce the number of phototherapy sessions and the cumulative dose of NBUVB [57].

Immunobullous diseases

In 1984, the unsuccessful use of isotretinoin in a single case of pemphigus vulgaris was reported [58].

In 2000, in a case of IgA pemphigus (subcorneal pustular dermatosis type), a satisfactory therapeutic response to a daily isotretinoin dose of 20 mg was reported [59].

BEXAROTENE IN CLINICAL DERMATOLOGY

Cutaneous T-cell lymphoma

Bexarotene is the first synthetic rexinoid. The anti-tumor effects of rexinoids could be mediated by RXR heterodimers (formed with RAR and peroxisome proliferator activated receptor (PPAR)). In CTCL, RXR–PPAR heterodimer blocks the proliferation of activated T-cells and the secretion of IL-2. Another mechanism proposed by Zhang *et al.* is the apoptosis of cell lines in cutaneous T-cell lymphoma (CTCL) [60-62]. The overall bexarotene antitumoral mechanism of action has not been fully understood yet. However, it seems that the immunological action of bexarotene in CTCL may be through the down-regulation of Th2 cytokines and the enhancement of Th1 response [63]. Bexarotene at a daily dose of 300 mg/m^2 has been shown to be effective in 15 out of 28 (54%) patients with refractory or persistent early stage CTCL and in 25 out of 56 (45%) patients with refractory advanced-stage CTCL [64]. Bexarotene is an FDA-approved oral treatment for CTCL; its efficacy has been shown in several studies [3,65-67]. Nearly most of the patients experience hypothyroidism and hyperlipidemia. These two adverse effects are reversible and manageable. The recommended initial dose is 300 mg/m^2/day taken in a single dose with the meal. If there is no tumor response after 8 weeks, it can be increased to 400 mg/m^2/day; careful monitoring is required due to the dose-dependent toxicity. Although bexarotene is an FDA-approved drug for CTCL therapy, it has recently been shown that acitretin is an effective and well-tolerated drug for the treatment of early-stage CTCL (comparable with bexarotene) [68]. Bexarotene is a pregnancy category X drug, so the female patients should use contraception during the treatment and 1 month after the discontinuation of the therapy [69]. Recently, a consensus for clinical prescribing of bexarotene has been published. For detailed information, interested clinicians are referred to this article [70].

SYSTEMIC RETINOIDS IN THE MANAGEMENT OF MYCOSES FUNGOIDES AND SÉZARY SYNDROME

The first and second generations of systemic retinoids (isotretinoin and acitretin) and bexarotene (a RXR selective retinoid) have been used in the treatment of mycoses fungoides (MF). The result of the treatment of MF using a combination of retinoids and PUVA (RePUVA) is comparable to treatment with PUVA alone. This combination also requires need for fewer sessions of treatment and a significantly lower cumulative dose of PUVA [71]. Bexarotene, an FDA-approved drug, is the most commonly used X receptor activator retinoid for the treatment of MF and Sézary syndrome. Bexarotene at a dose of 300 mg/m^2/day (average daily dose: 450-675 mg) has been used successfully for MF. It is recommended to use the capsules with the meal in the evening [72]. For Sézary syndrome, bexarotene has been recommended as a second line treatment (the first line therapy includes extracorporeal photopheresis with or without other systemic therapies) [73].

In a recent study, the long-term use of bexarotene (the longest duration of treatment: 65.2 months) in 20 patients with MF and 12 patients with Sézary syndrome was investigated (32 patients in total). In this study, 60% response rate for all patients and 75% response rate for patients with Sézary syndrome were observed. Although hypothyroidism, hypercholesterolemia and hypertriglyceridemia were observed in 94%, 44% and 78% of the patients respectively, the study showed that bexarotene was a well-tolerated drug for the long-term use [74]. Since bexarotene may not be available in all countries and also may not be affordable for some patients, acitretin, which is a well-tolerated drug, has been used as a successful adjuvant therapy in the early stages of MF instead of bexarotene [68].

In addition to the three systemic retinoids, oral alitretinoin has been recently used as an adjuvant in the treatment of MF and Sézary syndrome. There are three reports in which three cases with MF and one with Sézary syndrome have been successfully treated with alitretinoin in combination with other modalities [75-77]. The capability of alitretinoin to bind to the retinoid receptors, namely RAR and RXR, leads to the alteration in cell differentiation, proliferation and apoptosis, which results in the

antitumor activity [75]. In comparison with bexarotene, alitretinoin has fewer side effects (lower risk for mucocutaneous side effects and alterations in the laboratory test, such as an increase in serum lipids, liver enzymes and thyroid hormones). Accordingly, alitretinoin would be a part of CTCL management in the future. Treatment of CTCL with alitretinoin is beyond the subject of this review.

THE ADVERSE EFFECTS OF RETINOIDS

Mucocutaneous adverse effects

Mucocutaneous side effects are the most common adverse effects observed with oral retinoids and occur in a dose-dependent fashion. The reduction in sebum production, the alteration in the barrier function of the skin and the reduction in stratum corneum thickness which are all caused by retinoids are responsible for these side effects. Cheilitis is the most common and the earliest adverse effect. Xerosis has been reported in nearly 50% of the patients on isotretinoin therapy and it is even more common in patients with atopic diathesis [3]. Also, the occurrence of staphylococcal infection of the skin has been reported with isotretinoin therapy [2]. Mucocutaneous adverse effects may be less common with bexarotene [2].

In a study of 457 Iranian patients on etretinate therapy, cheilitis was the most common mucocutaneous side effect (88.1%). In this study, other adverse effects, in the order of frequency, were hair loss, dry mouth with thrush, dry mucosa, palmoplantar peeling, dry skin with pruritus, epistaxis, paronychia, facial dermatitis, conjunctivitis, hair color change, waving of hair and dyspareunia [78].

Systemic adverse effects

Hyperlipidemia

Hyperlipidemia is the most common systemic side effect of retinoids, which is often proportional to the dose and reverses 4-8 weeks after the discontinuation of the drug. The elevation of triglyceride is more pronounced and occurs in 50% of the patients taking isotretinoin or acitretin and 79% of those receiving bexarotene [3]. Hypertriglyceridemia is more likely to occur in patients with predisposing factors such as diabetes, obesity, alcohol intake, or a family history of these conditions. A concomitant increase in the total amount of cholesterol and low-density lipoprotein is also common. Bexarotene has been associated with a higher incidence of acute pancreatitis, as well [3]. Fulminant pancreatitis has also been reported with acitretin therapy [9].

In a study that evaluated 500 Iranian patients on etretinate therapy, 30.6% had hypertriglyceridemia [79]. The regular monitoring of fasting serum lipids is required during retinoid therapy (monthly for the first two months, and every 2-3 months thereafter). Bexarotene requires more intensive monitoring; a baseline serum lipid is required before initiating the therapy and every 1-2 weeks until the levels are stabilized [3].

Blood toxicity

Dose-dependent leukopenia has been reported within 2-4 weeks of bexarotene therapy in CTCL [9,80]. One case of agranulocytosis has been reported in a 15-year-old girl receiving isotretinoin [81,82]. In 1987, a case of thrombocytopenia was reported as a result of isotretinoin therapy. In this patient, the rechallenge of isotretinoin led to thrombocytopenia [82]. Thereafter, several other cases of thrombocytopenia caused by isotretinoin were also reported [83-85].

Renal effects

Retinoids are generally not associated with renal toxicity. Isotretinoin is safely used in end stage renal disease (ESRD) patients undergoing hemodialysis. However, there are some reports of reversible renal dysfunction while using etretinate. It is recommended to monitor the renal function in patients with underlying renal diseases [3].

Neuromuscular effects

Headache with or without benign intracranial hypertension, generalized muscle stiffness syndrome, epileptic seizures and myalgia have been reported with oral isotretinoin. Creatine phosphokinase has been found to be elevated with or without muscular symptoms in isotretinoin users. Muscle pains and cramps are also reported in patients receiving acitretin or etretinate. The occurrence of rhabdomyolysis and severe myopathy

has been rarely reported in patients with intense physical activity during isotretinoin therapy [3,86,87].

Bone toxicity

Osteoporosis is a well-known effect of chronic hypervitaminosis A [3]. Periosteal bone formation hyperostosis, resembling diffuse idiopathic skeletal hyperostosis (DISH) and premature epiphyseal closure in children have also been reported with chronic vitamin A toxicity [2]. Long-term treatment with etretinate (> 2 years) has been shown to decrease bone mineral densitometry (BMD) [88]. Eight of 10 children on etretinate therapy for keratinization disorders showed bone abnormalities (periosteal thickening, periosteal bone resorption, osteoporosis, disc narrowing, and slender long bones) [89]. According to a study by McMullen and his colleagues, acitretin is safe in terms of bone loss even in long-term use (>3 years) [90]. In 18 men, a decrease was reported in their bone density after 6 months of using 1 mg/kg of isotretinoin [91]. Some studies have shown that isotretinoin does not bear a significant risk of bone loss. In a multicenter study on 217 acne patients, a single course of isotretinoin therapy (1 mg/kg for 16 to 20 weeks) showed no clinically significant change in BMD values in adolescents [92]. According to a recent preliminary study, deficiency in vitamin D might be a risk factor for developing bone resorption and osteopenic women treated with short-course isotretinoin [93]. Skeletal hyperostosis has been observed in the patients treated with an isotretinoin dose of 2 mg/kg/day for keratinization disorders, a year after initiating the therapy [94,95]. Hyperostosis will become prominent through the time [95]. Other studies have shown skeletal hyperostosis to be present in patients receiving long-term therapy with high-dose isotretinoin (2 years or longer) [96]. The spinal changes are similar to DISH [96].

Multiple hyperostoses at extremities and spine including anterior spinal ligament calcification, osteophyte formation, and calcification of the tendons and ligaments have also been reported with etretinate and isotretinoin [3]. Recent studies suggest that the risk of hyperostosis with short-term treatment with isotretinoin remains minimal [97]. A single course of isotretinoin with a cumulative dose of 120 mg/kg for 4 to 6 months has no significant effect on bone metabolism [98]. The risk of DISH-like hyperostosis during conventional treatment with isotretinoin is limited [99].

Retinoid hyperostosis is age dependant; it is also related to the dosage and the duration of the therapy. Five years after retinoid therapy, hyperostosis can be observed in most of the patients [100].

Premature epiphyseal closure has been reported in children on etretinate and isotretinoin therapy [100,101]. It is related to the dose and the duration of the treatment [100]. The authors recommended that the children on long-term systemic retinoid therapy should be monitored for bone changes [89,101].

Alopecia

Alopecia and telogen effluvium due to the use of systemic retinoids have been reported [2,102]. Hair loss is more frequently seen with acitretin than with etretinate. It is also much less frequently reported with isotretinoin and bexarotene [2]. Hair loss is a dose-dependent effect and is reversible in 2 months after reducing the dose or discontinuing the treatment [2].

Ocular Toxicity

Blepharoconjunctivitis can occur in one third of the patients treated with isotretinoin. Using artificial tears and avoiding the use of contact lenses may prevent this side effect [9]. Decreasing the night vision appears to be the side effect of isotretinoin therapy [2].

Teratogenicity

For the first time, Cohlan reported teratogenicity due to high dose vitamin A [103]. Today, the teratogenetic potential of retinoids is well documented [96]. Isotretinoin, etretinate, acitretin, and bexarotene are all classified by FDA in category X and are absolutely contraindicated during pregnancy and lactation [43,69].

Retinoids have been associated with the following embryopathies: microcephaly, hydrocephalus, microphthalmos, micrognathia, cardiac septal defects and complex heart malformations, abnormalities of the ear and acral skeleton, craniofacial and thymus gland anomalies [41]. Furthermore, adverse pregnancy outcomes such as spontaneous abortion, premature birth or fetal death have been reported, as well [3].

Pregnancy should be excluded with at least one negative pregnancy test (two in the U.S.) 2-4 weeks before considering retinoid therapy and at regular intervals thereafter (e.g. monthly for isotretinoin) [3].

Adequate contraception (ideally two methods) is mandatory from at least one month prior to the administration of retinoids up to 1 month after the cessation of bexarotene therapy, 3 months after the cessation of the treatment with isotretinoin and 3 years (2 years in Europe) after the cessation of the treatment with acitretin [41]. Etretinate has been removed from the market because of its accumulation in adipose tissues [104]. There are few reports about fetus malformation due to the use of isotretinoin by males at the time of conception [2]. The available data do not suggest an increased risk of fetal anomalies due to paternal exposure to acitretin [2,105]. However, it is usually recommended that the men who are trying to father a child should avoid systemic retinoids [3].

BEXAROTENE-RELATED SIDE EFFECTS

Hypothyroidism

Clinical and subclinical secondary hypothyroidism (characterized by low serum TSH and thyroxine concentrations) are seen in 40% of the patients with CTCL treated with bexarotene [3,106]. Hypothyroidism is due to thyrotropin suppression by retinoid X receptor. It is more common with higher doses of bexarotene and is rapidly reversible after treatment cessation [3,60,106,107]. Hypothyroidism is most often clinically symptomatic and thyroxine replacement is required [107].

ISOTRETINOIN-RELATED SIDE EFFECTS

Effects on homocysteine and folate

Schulpis *et al.* showed that the plasma levels of homocysteine are significantly elevated after 45 days of treatment with isotretinoin in patients with cystic acne. This effect could be either due to the inhibition of cystathionine beta synthase by isotretinoin or isotretinoin-induced liver dysfunction. The authors recommended daily folate, vitamin B6 and B12 supplementation along with the frequent monitoring of blood levels to prevent homocysteine -associated premature occlusive vascular disease [108]. Chanson *et al.* showed that a 28-day supplementation program with isotretinoin decreased plasma folate in both young and old healthy individuals [109]. Since hyperhomocysteinemia and folate deficiency are known to be associated with fetal developmental abnormalities, obstructive vascular diseases, degenerative neurologic diseases, and even colorectal cancer, future studies addressing these concerns are required.

Mood Change and Psychiatric Effects

Mood change due to the oral use of isotretinoin is not accepted universally and remains a challenging subject for most of the dermatologists involved in isotretinoin therapy. In 1983, Hazen *et al.* reported depressive symptoms in 6 out of 110 patients treated with isotretinoin [110]. Bremner and his colleagues studied the influence of isotretinoin on the function of the brain by using positron emission tomography (PET) scan and concluded that isotretinoin decreased the brain metabolism in the orbitofrontal cortex. The orbitofrontal area of the brain cortex is known to mediate the symptoms of depression [111,112]. However, a large population-based cohort study found no evidence that the use of isotretinoin is associated with an increased risk for depression, suicide, or other psychiatric disorders [113]. In a systematic review, the rates of depression among isotretinoin users ranged from 1% to 11% across studies, with similar rates in oral antibiotic control groups. Some of these studies have reported a decrease in the incidence and severity of depression in the patients treated with isotretinoin [114]. To the best of our knowledge, Azoulay et al showed a significant association between depression and isotretinoin therapy in a controlled study for the first time [115].

Briefly, according to most authors, our present knowledge is not enough to establish a causal relationship between isotretinoin and suicidal behavior and/or depression [114-117]. However, according to a recent comprehensive review by Bremner *et al.* on the patients receiving isotretinoin, brain imaging studies showed a direct relationship between the decreased orbitofrontal function and headache [118]. On the other hand, in isotretinoin-treated patients, the patients with headache are more prone to depression [119]. As a conclusion, the patients with headache, the patients with a past

history of affective disorders, and the patients sensitive to the effects of isotretinoin on the central nervous system are more prone to depression.

Inflammatory bowel disease

There are anecdotal reports about isotretinoin therapy and inflammatory bowel disease. Two studies could not confirm the association between isotretinoin therapy and inflammatory bowel disease (IBD), especially chronic IBD [120,121]. A case-control study showed a relationship between ulcerative colitis (UC) and the use of isotretinoin [122]. The risk of UC is increased with higher doses of isotretinoin [122].

Acute generalized exanthematous pustulosis

In a white female, acute generalized exanthematous pustulosis has been reported due to a daily isotretinoin dose of 40 mg for treating hidradenitis suppurativa [123].

PREVENTING ADVERSE EFFECTS

In 1970, vitamin E was shown to have beneficial effects on hypervitaminosis A [124]. However, vitamin E has no preventive effects on the adverse reactions of isotretinoin or acitretin [125,126]. Partial relief of acitretin-associated palmoplantar peeling has been noted with Vitamin E [127].

DRUG INTERACTIONS

Generally, alcohol consumption increases the risk of retinoids side effects (especially with acitretin). The use of the following drugs with retinoids should be avoided: minocycline, tetracycline (risk of raised intracranial pressure), vitamin A supplement (hypervitaminosis A) and methotrexate (hepatotoxic synergies with retinoids). The anti-ovulatory effect of progestin pill is decreased by acitretin [16]. However, contraceptive pills have no negative influence on acitretin, etretinate, or isotretinoin [128]. Isotretinoin increases the clearance of carbamazepine; therefore, it is necessary to monitor the plasma levels of carbamazepine. A combination of isotretinoin or etretinate with cyclosporine has been anecdotally reported to increase the serum level of cyclosporine [3,128]. Since bexarotene is metabolized by cytochrome P450 3A4, inhibitors of cytochrome P450 such as ketoconazole, itraconazole, erythromycin, gemfibrozil, and grapefruit juice may lead to an increase in plasma bexarotene concentrations. Rifampin, phenytoin, phenobarbital, and other inducers of cytochrome P450 3A4 may cause a reduction in plasma bexarotene concentrations [129].

Retinoids are associated with increased insulin sensitivity and the concurrent use of retinoids and antidiabetic agents may lead to hypoglycemia [16]. The important drug interactions of retinoids are shown in Table 2 [16,128,130-133].

Table 2. Drug interactions with systemic retinoids

Drug name	Category	Interaction with retinoid
Methotrexate	Folate Antagonist	Risk of hepatotoxicity
Cyclosporine	Immunosuppressive	Serum level of cyclosporine is increased
Carbamazepine	Anticonvulsants	Serum level of retinoids is increased
Phenytoin	Anticonvulsants	Serum level of retinoids is increased
Phenobarbital	Anticonvulsants	Serum level of retinoids is increased
Gemfibrozil	---	Bexarotene may increase the serum level of gemfibrozil
Tetracycline	Antibiotics	May cause pseudo tumor cerebri
Doxycycline	Antibiotics	May cause pseudo tumor cerebri
Minocycline	Antibiotics	May cause pseudo tumor cerebri
Rifampicin	Antibiotics	Serum level of retinoids is decreased
Ketoconazole	Azoles	Increases plasma levels of bexarotene
Itraconazole	Azoles	Increases plasma levels of bexarotene
Ethanol	Alcohol	Conversion of acitretin to etretinate
Progestin minipill	Hormonal contraceptive	Reduced serum level of progesterone, contraception failure
Corticosteroids	Corticosteroids	Increase the risk of bone loss
Oral antidiabetic agents	Antidiabetic	Risk of hypoglycemia
Vitamin A	Vitamin	Hypervitaminosis A
Grape fruit juice	Fruit	May increase plasma levels of bexarotene

List of Abbreviations

Activator Protein	AP
All-trans Retinoic Acid	ATRA
Bone Mineral Densitometry	BMD
Cytosolic Retinoic Acid Binding Protein	CRABP
Diffuse Idiopathic Skeletal Hyperostosis	DISH
Food and Drug Administration	FDA
Psoriasis Area and Severity Index	PASI
Positron Emission Tomography	PET
Peroxisome Proliferator Activated Receptor	PPAR
Psoralen and Ultraviolet A	PUVA
Retinoic Acid Receptor	RAR
Retinoic Acid–Response Elements	RARE
Retinoid X Receptors	RXR
Therapeutic Index	TI
Vitamin D Receptor	VDR

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