

# Chapter 2

## Vitamin A and the Skin

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### Core Messages

- Vitamin A (vit. A) is essential for normal differentiation and maintenance of epithelial tissues in skin and mucous membranes, vision (retinaldehyde), reproduction (retinol), and embryonic morphogenesis.
- Retinoids (compounds with biological activities similar to those of vit. A) are used as therapeutic agents for hyperkeratotic and parakeratotic skin diseases, acne and acne-related disorders, and hand eczema. They are also used as prophylaxis for epithelial skin tumors in immune-suppressed patients and as therapy for non-melanoma skin cancers and cutaneous T-cell lymphoma.
- Regular monitoring is essential for the avoidance and management of a wide range of adverse effects.

### 2.1 Introduction

Retinoids refer to compounds that have biological activities similar to those of naturally occurring vitamin A (vit. A) but not necessarily the same chemical structure (Zouboulis and Orfanos 2000). The definition of retinoids does not include a structural homology to vit. A. Retinoids are used as therapy and prophylaxis systemically or as local applications for various skin diseases and tumors. They are also used in the cosmetic field for acne, seborrhea, psoriasis, epithelial tumors, and hand eczema. Retinoids perform their actions through binding to

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retinoid receptors (RAR and RXR), members of the hormone nuclear receptor subfamily. In addition to its toxicity, a deficiency of vit. A causes skin manifestations. Owing to the wide range of adverse effects of retinoids, precautions and regular monitoring are essential for long-term therapy.

## 2.2 Naturally Occurring Retinoids

Natural retinoids include vit. A (retinol) and its metabolic derivatives retinaldehyde and retinoic acid (Zouboulis and Orfanos 2000). The normal concentration of vit. A in plasma is 0.35–0.75  $\mu\text{g/mL}$ . Retinoic acid is produced by *in vivo* oxidation of retinol. Its two isoforms are all-trans retinoic acid and 13-*cis* retinoic acid, with normal plasma concentrations of 0.55–1.20 and 0.80–2.40  $\text{ng/mL}$ , respectively. Retinoic acid can fully substitute for retinol, except for maintaining reproduction. Daily requirement of vit. A is 0.8–1.0 mg (2,400–3,000 IU), which can be found in ten medium-sized eggs or 100 g of butter. Hypervitaminosis occurs with intake of more than 18,000–60,000 IU vit. A per day for children and 50,000–1,00,000 IU for adults. Higher uptakes usually do not result in elevated retinol levels, however the stored retinol esters level are increased wherever retinol esters are stored.

## 2.3 Synthetic Retinoids

The synthetic retinoids (Table 2.1) are either chemical modifications of naturally occurring vit. A or chemically different compounds with the capacity to bind or antagonize retinoid nuclear receptor proteins (Zouboulis and Orfanos 2000). Nonaromatic, monoaromatic, and polyaromatic compounds have been developed through chemical modification. Modification of the polyene chain diminishes bioactivity; modification or esterification of the carboxylic end diminishes the toxicity while maintaining the activity; and ring substitution diminishes the toxicity and markedly increases the activity.

## 2.4 Absorption, Distribution, and Metabolism

The oral bioavailability of retinoids can be increased, especially by fatty acids, which prevent the binding of retinoids with albumin and hence improve the clinical effect (Avis et al. 1995). The metabolism of retinoids generally occurs in the liver. It involves oxidation and chain shortening to produce biologically inactive metabolites. Retinoids are excreted through feces and urine.

Isotretinoin is detectable after 30 min in blood, and maximum concentrations are reached 2–4 h after oral intake (Ganceviciene and Zouboulis 2007). The half-life elimination rate of isotretinoin ranges from 7 to 37 h, and that of its known

**Table 2.1** Synthetic retinoids in current use

Chemical structure	Generic name	Initial trade name	Approved medical use
First generation			
All-trans retinoic acid	Tretinoin	Retin-A	Topical treatment of acne vulgaris, photodamage
9- <i>cis</i> retinoic acid	Alitretinoin	Vesanoid	Systemic treatment of acute promyelocytic leukemia
		Toctino	Systemic treatment of therapy-resistant hand eczema
		Panrelin	Topical treatment of AIDS-associated Kaposi sarcoma
13- <i>cis</i> retinoic acid	Isotretinoin	Accutane	Systemic treatment of severe recalcitrant acne and acne-related dermatoses
		Isotrex	Topical treatment of acne
Second generation			
Monoaromatic compound	Etretinate	Tigason	Systemic treatment of psoriasis
Etretinate derivative	Motretinide	Tasmaderm	Topical treatment of acne vulgaris
Free acid metabolite of etretinate	Acitretin	Neotigason	Systemic treatment of psoriasis and severe disorders of keratinization
Third generation			
Polyaromatic retinoids (retinoids)	Adapalene	Differin	Topical treatment of acne
	Tazarotene	Tazorac	Topical treatment of plaque-type psoriasis, acne vulgaris, and photodamage
	Bexarotene	Targretin	Systemic treatment of cutaneous T-cell lymphoma, breast cancer, and Kaposi sarcoma
			Topical treatment of cutaneous T-cell lymphoma

metabolites is 11–50 h (Benifla et al. 1995). The major metabolites of isotretinoin in blood are 4-oxo- and 4-hydroxy-isotretinoin; several glucuronide conjugates are detectable in bile (Vane et al. 1990). Because there is interconversion between the two isomers, isotretinoin and tretinoin, in vivo, about 10–30% of the drug is metabolized via tretinoin. Isotretinoin is excreted in feces after conjugation or in urine after metabolization. In contrast to vit. A, there is neither liver nor adipose tissue storage. More than 99% of isotretinoin in plasma is bound to plasma proteins, mainly albumin (Rollman and Vahlquist 1986). Serum albumin has a critical function as a retinoid-binding protein in reducing the concentration of active retinoids and restricting the biological effects on sebaceous gland cells (Tsukada et al. 2002). After discontinuation of therapy, isotretinoin disappears from serum and skin within 2–4 weeks. It seems likely that isotretinoin therapy interferes with the endogenous metabolism of vit. A in the skin because vit. A levels increased by about 50% and dehydrovitamin A levels decreased by around 80% in some patients (Orfanos and Zouboulis 1998).

Acitretin is eliminated more rapidly than etretinate. Etretinate is highly lipophilic, binds strongly to albumin, is stored in adipose tissue, and is released slowly (half-life of 120 days), whereas the half-life of acitretin is only 2 days. Reesterification of acitretin to etretinate occurs only in cases of alcohol consumption (Wiegand and Chou 1998).

Bexarotene in plasma is 99% bound to plasma proteins. It is excreted via the hepatobiliary system, and its terminal half-life is 7–9 h (Ethan Quan and Wolverton 2003).

## 2.5 Mechanism of Action

### 2.5.1 Retinoid Receptors and Gene Regulation

Retinoids enter the cell by non-receptor-mediated endocytosis, interact with cytosolic proteins, and finally bind to nuclear receptors. The retinoid nuclear receptors are members of the steroid thyroid hormone receptor superfamily. Retinoid A receptors (RAR) bind all-trans retinoic acid and 9-*cis* retinoic acid with high affinity, whereas they barely bind to 13-*cis* retinoic acid. Retinoid X receptors (RXR) also bind 9-*cis* retinoic acid and are selective for bexarotene, which is a specific RXR ligand (retinoid). 14-Hydroxy-retro-retinol does not bind or activate retinoid receptors, whereas acitretin does not bind but does activate RAR.

The RAR and RXR families each include three members:  $\alpha$ ,  $\beta$ ,  $\gamma$ . Each receptor is mapped on a different chromosome. High expression of RAR- $\gamma$  and RXR- $\alpha$  was detected in healthy and psoriatic epidermis, as well as in sebaceous gland cells.

Retinoid receptors target and regulate the genes that have retinoid-responsive elements (RARE and RXRE) in their promoter regions. The retinoid receptor–gene interaction occurs because RAR genes have retinoid-responsive elements, which

allow a positive feedback mechanism. On the other hand, the retinoid-binding proteins may antagonize the retinoid interaction with their nuclear receptors. Specific retinoid effects can occur via interaction of retinoid receptors with other signal transduction mechanisms.

### ***2.5.2 Effect on Epidermal Growth and Differentiation***

Retinoids promote cell proliferation in normal epithelia, whereas they normalize it in hyperproliferative conditions. Retinoids induce and modulate the expression of growth factors and their receptors. Keratinocyte proliferation by retinoids is mediated through induction of cyclic adenosine monophosphate (cAMP), epidermal growth factor (EGF) receptor binding, protein kinase C (PKC), and transforming growth factor- $\alpha$  (TGF $\alpha$ ). Retinoids down-regulate cell growth which is mediated by a TGF $\beta$ 2-regulated inhibition of the EGF binding to its receptor. Retinoids have also a keratolytic effect through shifting the terminal keratinocyte differentiation toward a nonkeratinizing mucosa such as epithelium. As for differentiation, retinoic acids down-regulate most of the markers of terminal differentiation in vitro (loricrin, transglutaminase, involucrin, filaggrin, keratins 1 and 10), whereas keratins 19 and 13, the markers of nonstratified and wet epithelia, are up-regulated. Adapalene and retinoic acid restore the architecture of epidermis and antagonize hyperkeratosis. RAR- $\alpha$  receptor agonists promote differentiation in T47D breast carcinoma cells in vitro.

### ***2.5.3 Effects on Sebaceous Gland Activity***

See the section Seborrhea, Acne, and Acneiform Disorders later in the chapter.

### ***2.5.4 Immunomodulatory and Antiinflammatory Properties***

Isotretinoin, etretinate, and acitretin were proved to inhibit angiogenesis both in vitro and in vivo (in mice with T47D cell-induced tumors) most probably through RAR- $\alpha$ . Retinoids can stimulate humoral and cellular immunity through enhancing antibody production, increasing blood T-helper cells, and preventing Langerhans cells depletion from epidermis by ultraviolet (UV) light and in vitro increasing cell surface antigens of T and natural killer cells. Antiinflammatory activity of retinoids has also been shown. Inhibition of neutrophil migration in psoriatic skin, inhibiting LTB<sub>4</sub>-induced migration of neutrophils (topical isotretinoin more than tretinoin or retinoids), and inhibition of nitric oxide and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) production have been reported.

## 2.6 Therapeutic Uses

### 2.6.1 Psoriasis and Related Disorders

The orally administered aromatic retinoids (etretinate and acitretin) are used to treat psoriasis, both initially and for maintenance. Retinoids have a synergistic effect with other psoriasis treatment modalities. They are considered the drug of choice in cases of pustular psoriasis and palmoplantar psoriasis. Retinoids were found effective in the juvenile types of pityriasis rubra pilaris. Retinoids act on both the epidermal and dermal levels to exhibit their antipsoriatic action. They reduce proliferation, enhance differentiation, regulate the desquamation of the corneocytes, modulate lymphocyte function, and inhibit neutrophil migration.

The daily dose of acitretin is 0.5 mg/kg body weight divided into two administrations to avoid serum peaks and complications (Table 2.2). Taking acitretin with meals that include some fat increases the blood absorption two- to fivefold. Retinoids being metabolized in the liver interact with ketoconazole and phenytoin but not with oral contraceptives.

### 2.6.2 Disorders of Keratinization

Etretinate and acetretin are superior to isotretinoin because of the latter's sebum-drying property. The severity of Darier's disease, ichthyosis vulgaris, congenital ichthyosis, and palmoplantar keratodermas can be successfully controlled with retinoids. Usually the treatment is prescribed with a low dose (0.2–0.5 mg/kg/day); a lifelong maintenance dose is required with long-term contraception and control of

**Table 2.2** Doses of acitretin and therapeutic effect

Disease	Dose	Duration of therapy
Pustular psoriasis	High initial dose (0.5–1.0 mg/kg) reduced to 0.20–0.25 mg/kg over 3–6 months	Maintenance 6–12 months
Erythrodermic psoriasis	Low initial dose (0.20–0.25 mg/kg) increased to 0.5–0.6 mg/kg over 3 months	Maintenance 6 months
Plaque-type psoriasis		
Monotherapy or combined with anthraline or topical steroids	0.3–1.0 mg/kg/day	4–12 weeks
With UVB	0.2–0.5 mg/kg/day	6 weeks
With PUVA	0.2–0.5 mg/kg/day	4–6 weeks

UVB ultraviolet B radiation; PUVA psoralen + ultraviolet A radiation

bone density to avoid bone toxicity. Interestingly, other keratinization disorders such as pachyonychia congenita, inflammatory linear verrucous epidermal (ILVEN) nevus, Netherton's syndrome, and monilethrix do not respond to retinoids,

### 2.6.3 *Seborrhea, Acne, and Acneiform Disorders*

Isotretinoin proved to be the most effective sebostatic retinoid both in vivo and in cell cultures; and it is the best retinoid for treating severe acne (Zouboulis and Orfanos 2000). Although it shows low binding affinity for intracellular retinoid-binding proteins and for RAR and RXR, isotretinoin has strong sebostatic activity. It undergoes a specific and selective intracellular isomerization process into tretinoin, which in turn binds to RARs. The superior sebostatic effect of isotretinoin over tretinoin (its metabolite) is attributed to the delayed initiation of inactivation of isotretinoin; incubation of sebocytes with tretinoin leads to rapid enhancement of cellular retinoic acid-binding protein levels, which promotes the metabolism by cytochrome P 450 enzymes (Tsukada et al. 2000). It was also found that isotretinoin inhibits  $3\alpha$ -hydroxysteroid oxidation, leading to decreased levels of dihydrotestosterone and androstenedione, which may contribute to the sebosuppressive effect (Guy et al. 1996; Karlsson et al. 2003). Lipogenesis is also reduced by TGF $\beta$ 2 and TGF $\beta$ 3, which are rapidly and transiently expressed as a response to retinoid administration (Downie et al. 2002). Isotretinoin decreases sebum production, decreases the number of proliferating sebocytes and the size of the sebaceous gland, inhibits sebocyte differentiation in vivo and in vitro (Orfanos et al. 1997; Zouboulis et al. 2000; Ganceviciene and Zouboulis 2007), and directly suppresses abnormal desquamation of sebaceous follicles. Isotretinoin thus alters the follicular microenvironment via its sebostatic effect and hence markedly reduces the *Propionibacterium acnes* count (King et al. 1982). It also has immunosuppressive and antifibrosis effects when tested on renal allografts (Adams et al. 2005). Through RAR-independent mechanisms, it was associated with cell cycle arrest, induction of apoptosis, decreased proliferation, decreased lipogenesis rate, and decreased DNA synthesis (Zouboulis et al. 1993; Nelson et al. 2006; Zouboulis 2006a). Isotretinoin acts in a receptor-independent manner by influencing cellular signaling pathways through direct protein interactions or by enzyme inhibition (Imam et al. 2001).

Isotretinoin reduces monocyte and neutrophil chemotaxis and their migration to the epidermis, minimizing the excessive inflammation that causes scarring (Zouboulis 2006a). The matrix metalloproteinases (MMPs) were found to be elevated in acne lesions, raising a possibility of involvement in acne pathophysiology through mediation of inflammation and collagen degradation. Isotretinoin induced reduction of Pro-MMP-9 and MMP-13 (Papakonstantinou et al. 2005). Isotretinoin has a strong influence on sebaceous lipid composition, as it decreases wax esters, triglyceride fractions, and squalene; it relatively increases the cholesterol level and the levels of free sterols and total ceramides (Orfanos and Zouboulis 1998).

### 2.6.3.1 Dosing, Therapeutic Effect, and Monitoring

The required dose is 0.5 mg/kg/day, an initially high dose for 3 months; maintenance requires a lower dose. A cumulative dose of more than 150 mg/kg administered over 6–12 months has been considered necessary to ensure a long-lasting remission (Zouboulis and Piquero-Martin 2003). Owing to relevant recurrence rates, current treatment concepts individualize dosage and duration (Zouboulis 2006b). Longer treatment duration might be needed in patients with extrafacial lesions, low-dose therapy, or severe acne. Contraception is essential during treatment with isotretinoin, and using an antiandrogen-containing contraception is of a great value (Zouboulis and Rabe 2010).

The European directive recommendations for the use of isotretinoin for treatment of acne note that treatment should start at 0.5 mg/kg, and that it should be used only for severe acne (nodular or conglobata) that is not responding to antibiotics or topical therapy; it should not be used as a first-line treatment. It is not recommended in children under 12 years of age. The liver enzymes and serum lipids should be checked before therapy, 1 month after its initiation, and every 3 months after that. All forms of peeling and wax depilation should be avoided during therapy and 6 months afterward. The pregnancy-preventing program for female patients during their childbearing period includes a medically supervised pregnancy test before, during, and 5 weeks after therapy begins. The test should be repeated monthly, and double contraception should be used. Only 30 days of oral isotretinoin can be supplied to female patients at a time (Layton et al. 2006).

### 2.6.3.2 Retinoid Local Therapy in Acne

Tretinoin, isotretinoin, motretinide, adapalene, and tazarotene are used for the local therapy of acne. Retinaldehyde, retinol, and retinyl esters, however, are used in cosmetic preparations. Early use of retinoids is recommended (Gollnick et al. 2003). Topical retinoids were found to perform their therapeutic action by increasing follicular epithelium turnover, reversing abnormal desquamation of the sebaceous duct. Hence the mature comedones are expelled and formation of microcomedones is inhibited; moreover, the aerobic follicular environment no longer favors the growth of *Propionibacterium acnes* (Lavker et al. 1992; Thielitz et al. 2007). Retinoids also show immunomodulatory activities (Bikowski 2005; Jones 2005).

Tretinoin and isotretinoin can be used alone or in combination with topical erythromycin, clindamycin, or benzoyl peroxide in different concentrations (Mills and Kligman 1978; Korting and Braun-Falco 1989; Marazzi et al. 2002).

Adapalene 0.1% was proved to have the same efficacy as tretinoin 0.025% but with more rapid onset of action (Cunliffe et al. 1998). Adapalene was also used in combination with clindamycin 1%, benzoylperoxide, or both (Zhang et al. 2004; Thiboutot et al. 2007; Del Rosso 2007). Addition of adapalene local therapy to the systemic doxycycline 100 mg/day significantly raised its efficacy (Thiboutot et al. 2005).

Tazarotene, which has been approved for topical acne treatment only in the United States, showed a stronger reduction in disease severity than adapalene but with

slightly higher irritation (Webster et al. 2002). Also, as for other topical retinoids, the combination with clindamycin or benzoyl peroxide (BPO) showed better efficacy (Tanghetti et al. 2006).

Maintenance therapy is required for a chronic disease such as acne. The use of tazarotene gel alone proved to be as effective as a combination of tazarotene and minocycline 100 mg/day but without the side effects of the systemic antibiotic (Zhang et al. 2004). Topical adapalene is also adequate for maintenance treatment.

## 2.6.4 Retinoids in Skin Cancer

### 2.6.4.1 Prevention of Keratinocyte Skin Cancers

Retinoids are used for chemoprevention and chemosuppression in many diseases and syndromes with high susceptibility of nonmelanoma skin cancer development (Abdel Naser and Zouboulis 2010; Nguyen and Wolverson 2000). Retinoids regulate MMPs, TGF $\beta$ , cyclin-dependent kinase 1, P16, and P21; hence, they are capable of regulating tumor stroma production and control tumor progression and invasion (Ayer et al. 1995; Hassig et al. 1997). RAR-related antiproliferative and proapoptotic signals may also be involved (Sun et al. 2000). Inhibition of the AP-1 complex, suppression of cyclooxygenase-2 (COX-2) expression, and inhibition of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesis are all involved in the reduction of cell proliferation (Fanjul et al. 1994; Kanekura et al. 2000). Specific indications of using retinoids in tumor prevention and suppression include patients with xeroderma pigmentosum, epidermodysplasia verruciformis, basal cell nevus syndrome (Gorlin-Goltz), or Bazex and Rhombo syndromes as well as individuals under immune suppression for organ transplantation (Shuttleworth et al. 1988; Otley et al. 2006).

Isotretinoin, because of its short half life, is the treatment of choice in young patients with xeroderma pigmentosum. Acitretin and etretinate are used in older patients and organ transplantation recipients who exhibited five or more low-risk squamous cell carcinomas (SCCs) per year, two or more high-risk SCCs per year, or systemic SCC (Kovach et al. 2006). Bexarotene (300 mg/m<sup>2</sup>/day) is the choice for cutaneous T-cell lymphoma (CTCL) (Duvic et al. 2001a, b). The treatment should be continued indefinitely, as discontinuation is associated with a rebound increase in skin cancer frequency (Kraemer et al. 1988; Goldberg et al. 1989). Large doses are required for chemosuppressive and preventive effects (isotretinoin 2 mg/kg/day, maintenance dose 1.5 mg/kg/day) (Lippman et al. 1987; Shuttleworth et al. 1988); therefore, close monitoring is essential. A combination of topical tretinoin and a low-dose etretinate (10 mg/day) may reduce the adverse effects of oral medication (Rook et al. 1995). The indications must be carefully assessed to outweigh the wide range of complications and adverse effects. On the other hand, isotretinoin plus interferon- $\alpha$  for adjuvant therapy of aggressive skin SCC showed high rates of tumor recurrence and second primary tumors (Brewster et al. 2007).

### **2.6.4.2 Therapy of Other Skin Cancers**

Melanoma was proved to be nonsensitive to retinoids. Bexarotene gel was introduced as a monotherapy for treatment of CTCL in early stages (IA, IB, IIA), which were refractory or intolerant to at least two other treatment modalities for more than 6 months (Zouboulis 2001). Bexarotene was found to induce a 50% overall inhibitory response in patients with refractory or persistent CTCL when administered either orally or topically with minimal toxicity. The use of oral bexarotene first to reduce dermal infiltrates prior to DAB(389)IL-2 (denileukin difitox) administration might reduce subsequent side effects imparted by this therapy (Duvic 2000).

Alitretinoin, as a 0.1% gel, was introduced as an adjuvant topical regimen for Kaposi sarcoma associated with acquired immunodeficiency syndrome (AIDS) (Walmsley et al. 1999).

### **2.6.5 Chronic Hand Eczema**

Eczema of the hands is a relatively common disease, seen in 6–8% of the population. Alitretinoin given at well-tolerated doses induces substantial clearing of chronic hand dermatitis in patients refractory to conventional topical therapy (Thomas et al. 2004).

Oral alitretinoin induced clinically significant responses in a high percentage of patients with moderate or severe chronic hand dermatitis refractory to standard topical therapy. Complete or near-complete disappearance of disease signs and symptoms was reported for 53% of patients treated with the highest alitretinoin dose (40 mg/day). The response was reported with all types of chronic hand eczema. Treatment is generally tolerated, with the typical retinoid adverse effects at the highest dose (headache, flushing, elevated serum fat levels) (Ruzicka et al. 2004). The mechanism of action of alitretinoin for chronic hand eczema may be explained by the fact that alitretinoin is a panretinoid agonist activating RXRs and RARs, mediating the stimulation of Th2 immune function (Bollag and Ott 1999; Stephensen et al. 2002). Bexarotene, applied topically in 1% concentration also proved to be effective for treatment of chronic hand eczema (Hanifi et al. 2004).

## **2.7 Adverse Reactions and Tolerability**

### **2.7.1 Mucocutaneous Complications**

The most common complication associated with retinoids is skin and mucous membrane dryness, including cheilitis, which occurs in about 90% of cases; it is an indication of good absorption. Mucocutaneous xerosis (30%), nosebleeds (15%), mild hair loss, augmented skin fragility, and palmoplantar desquamation (80%) are

additional adverse effects. The use of skin emollients, artificial eye tears, Vaseline for the inner part of the nose, and moisturizers for the lips are a necessity from the start of the treatment to avoid the dry skin complications. In the case of extensive dryness, reducing the dose by 25% can be of great help (Otley et al. 2006). Capillary leak syndrome, a rare complication that leads to face or generalized edema, was also reported (Estival et al. 2004; Scheinfeld and Bangalore 2006).

### ***2.7.2 Ocular and Neurological Complications***

Decreased tear production and decreased lipid content of the tear film lead to dryness of the eyes, and keratitis and corneal erosions can occur. The use of contact lenses is contraindicated, and artificial tears are mandatory. Other complications include blurred vision, decreased vision, photophobia, decreased dark adaptation, papilledema, corneal opacities, and retinal dysfunction. Blepharoconjunctivitis, which may be complicated with *Staphylococcus* infection, occurs in 20–50% of cases.

Pseudotumor cerebri (benign intracranial hypertension) is the most important neurological side effect. It manifests as headache accompanied by nausea, vomiting, and visual changes due to papilledema. Half of the reported patients were taking tetracycline or minocycline concomitantly with isotretinoin. Although depression, irritability, and suicidal intentions have been reported, a causal relation has not been demonstrated (Gold et al. 1989; Enders and Enders 2003; Scheinfeld and Bangalore 2006).

The most frequent central nervous system adverse effect associated with oral isotretinoin is headache, either as an independent adverse effect or as part of benign intracranial hypertension. Isolated cases of stiff-person-like syndrome, epileptic seizures, and generalized muscle stiffness syndrome possibly or probably related to oral treatment with isotretinoin have been reported (Chroni et al. 2010).

### ***2.7.3 Serum Lipids, Gastrointestinal Side Effects, Liver Function, and Endocrine Adverse Effects***

Increased serum lipids—hypertriglyceridemia (20–40%) being more common than hypercholesterolemia (10–30%) (Olsen et al. 1989; Barth et al. 1993)—with decreased high-density lipoprotein and increased low-density lipoproteinemia as well as mild transaminase increase are characteristic metabolic side effects of retinoids. Lipid profile changes are more likely to occur in patients with predisposing factors as obesity, familial hyperlipidemia, nicotine abuse, and diabetes as well as in patients using  $\beta$ -blockers and contraceptive pills (Orfanos et al. 1997). These changes are proportionate to the dose and reversible within 1–2 months (Gupta et al. 1989). Nausea, diarrhea, and abdominal pain may occur. Hyperlipidemia can be

avoided to an extent by ingesting a low-fat diet and by hypolipidemic drugs when needed. Chronic liver toxicity is rather rare, although acutely elevated liver enzymes is not uncommon mostly occurring with etretinate (Zane et al. 2006).

Monitoring of the liver enzymes and blood lipids according to the “European directive for prescribing systemic isotretinoin for acne vulgaris” must be done before the beginning of the therapy, after 1 month, and subsequently every 3 months. The concomitant use of methotrexate (in cases of acitretin treatment of psoriasis) or other drugs that affect the liver must be avoided. If the liver enzymes are elevated one- to threefold over normal levels, the therapy should be continued with 50% of the dose and the enzymes reevaluated in 2 weeks. Discontinuing the therapy is advised when liver function tests are three times normal, followed by a regular enzyme checkup every 2 weeks. Reintroduction is recommended after enzyme level normalization with 25% of the original dose (Otley et al. 2006).

Bexarotene causes significant central hypothyroidism (Haugen 2009) and hyperlipidemia in most patients managed with thyroid replacement and hypolipidemic drugs, respectively (Abbott et al. 2009). Hypothyroidism is in part due to increased peripheral thyroid hormone metabolism (Smit et al. 2007).

#### ***2.7.4 Long-Term Toxicity: Bone Changes***

The long-term bone toxicity occurs mostly with vitamin A chronic toxicity. The changes include hyperostosis and periostosis, demineralization, thinning of the bones, and premature epiphysial closure (Biesalski 1989). Radiography of significantly symptomatic joints is recommended with long-term therapy. Yearly radiography of the ankle or thoracic spine is optional (Otley et al. 2006; Scheinfeld and Bangalore 2006).

#### ***2.7.5 Arthralgias and Myalgias***

Diffuse idiopathic skeletal hyperostosis-like hyperostosis, lesions mimicking seronegative spondyloarthritis, arthralgia, myalgia, stiffness, true myopathy, muscular damage, rhabdomyolysis, and musculoskeletal pain can occur under retinoid treatment, especially isotretinoin. Creatine phosphokinase, a specific marker of muscle destruction, has been found to be elevated, occasionally by up to 100 times the normal value (with or without muscular symptoms and signs) in a variable percentage of patients receiving isotretinoin treatment and particularly in those undergoing vigorous physical exercise. Oral acitretin has been found to cause peripheral nerve dysfunction, particularly of sensory fibers, which in rare cases leads to clinically evident sensory disturbances. Less clear is the causal relation between acitretin and benign intracranial hypertension or myopathy, whereas an isolated case of cranial nerve IV (oculomotor) palsy and another case of thrombotic stroke during treatment with oral acitretin have been reported (Chroni et al. 2010).

Systemic diseases with involvement of nervous and/or muscle tissue and neuromuscular disorders should be regarded as exclusion criteria for initiation of oral retinoid therapy. Additionally, intense physical exercise and concurrent treatment with neurotoxic or myotoxic drugs should be avoided during treatment with oral retinoids (Chroni et al. 2010). When arthralgias and myalgias occur, it is recommended that the dose be decreased by 25% until the symptoms resolve (Otley et al. 2006).

### 2.7.6 Teratogenicity

Retinoids freely cross the placenta, causing severe fatal fetal malformations including craniofacial deformities, bone and cardiovascular abnormalities, and endocrine malfunctions. All systemic retinoid treatments are contraindicated during pregnancy (U.S. Food and Drug Administration category X). Exclusion of pregnancy before starting therapy and contraception during the therapy is mandatory. Contraception should be continued for 1 month after cessation of the retinoid therapy (isotretinoin and bexarotene) and for 3 years after acitretin. Topical retinoids are also contraindicated.

The pregnancy-preventing program for female patients during their child-bearing period is strictly applied to isotretinoin therapy. This includes a medically supervised pregnancy test before, during, and 5 weeks after therapy begins. The test should be repeated monthly, and double contraception should be used. For female patients, only 30 days of oral isotretinoin can be supplied at a time (Layton et al. 2006).

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