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Chapter 229

Retinoids

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Retinoids include both naturally occurring molecules and synthetic compounds that have specific biologic activities that resemble those of vitamin A or bind to the nuclear receptors for retinoids. Vitamin A from natural sources was already being used in the 1930s in high dosages to treat certain hyperkeratotic diseases, often with toxic side effects. Three generations of synthetic retinoids have since been developed (Fig. 229-1):

First generation: All-*trans* retinoic acid (tretinoin, ATRA), a naturally occurring metabolite of retinol, was the first retinoid synthesized but had no significant advantages over vitamin A in treatment of dermatologic diseases. It is used as a differentiation-inducing agent to treat acute promyelocytic leukemia.

Isotretinoin (13-*cis* retinoic acid), clinically available since the 1970s, was found to cause prolonged remissions in patients with previously treatment-resistant cystic acne [it has been approved by the U.S. Food and Drug Administration (FDA) for this indication since 1982].¹

Second generation: Through replacement of the B-ionone ring in ATRA with an aromatic structure, newer retinoids with better therapeutic margins were synthesized in the 1970s. Etretinate and its free acid metabolite, acitretin, showed a therapeutic index 10 times more favorable than that of ATRA. Etretinate (approved in Europe 1983 and by the FDA in 1987) and acitretin (approved 1987 and 1997, respectively) became a standard treatment for psoriasis.

Third generation: The discovery of retinoic acid receptors (RARs)^{2,3} allowed research directed toward receptor-specific, third-generation retinoids with a safer therapeutic index and a more selective action. Bexarotene, approved by the FDA in 1999 for systemic use in treating cutaneous T-cell lymphoma (CTCL), is a prime example. Bexarotene belongs to a subclass of arotinoids called *rexinoids*, because they bind to the retinoid X receptors (see Bexarotene).

▪ MECHANISM OF ACTION

Retinoids affect cell growth and differentiation, exert immunomodulatory action, and alter cellular adhesiveness.⁴ Their effect on RARs is discussed in detail in Chap. 217.

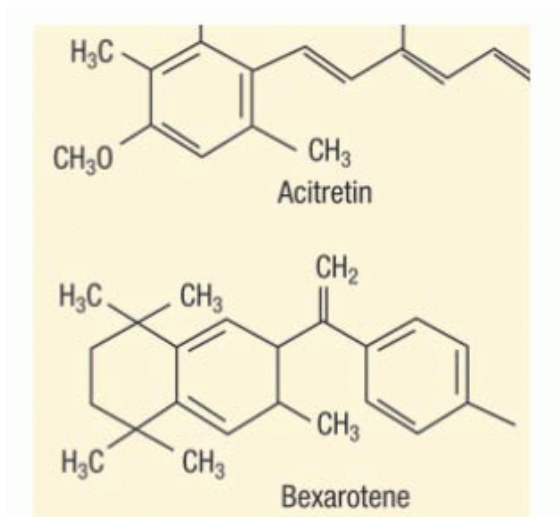
Under normal conditions, virtually all effects of vitamin A in the skin are mediated by ATRA, the cellular level of which is meticulously controlled. Endogenous ATRA has been at the focus in the development of a

new class of compounds called *retinoic acid metabolism-blocking agents*, which are basically cytochrome P₄₅₀ (CYP) enzyme 26 inhibitors

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that impede the oxidative degradation of ATRA and thus increase the retinoid activity in target tissues.⁵ Two such drugs (liarazole and Rambazole) are under development.

RETINOIDS AT A GLANCE



- The biologic functions and actions of retinoids (excluding vision) include the following:
 - Reproduction, embryonic growth, and morphogenesis
 - Modulation of proliferation and differentiation of epithelia
 - Decrease in sebaceous gland size (isotretinoin)
 - Immunologic and anti-inflammatory effects
 - Tumor prevention and treatment
 - Effect on extracellular matrix components
- Three types of oral retinoids and the major indication for their use are isotretinoin (acne), acitretin (psoriasis, keratinizing disorders), and bexarotene (cutaneous T-cell lymphoma). Contraindications to their use include pregnancy, breast-feeding, and non-adherence to contraceptive regimen.
- Mucocutaneous side effects (cheilitis, xerosis, skin peeling, conjunctivitis) are common, as are reversible abnormal results on laboratory tests [hyperlipidemia, increased liver enzyme levels, and hypothyroidism (bexarotene)]. Musculoskeletal and central nervous system side effects are rare.

■ PHARMACOKINETICS

Isotretinoin, acitretin/etretinate, and bexarotene differ not only in their spectra of clinical efficacy but also in their toxicities and pharmacokinetics. Due to their lipophilicity, the oral bioavailability of all retinoids is enhanced when they are administered with food, especially with fatty meals. Retinoids are metabolized mainly by oxidation and chain shortening to biologically inactive and hydrophilic metabolites, which facilitates biliary and/or renal elimination. The oxidative metabolism is induced primarily by the retinoids themselves and other agents that induce hepatic CYP isoforms.⁶

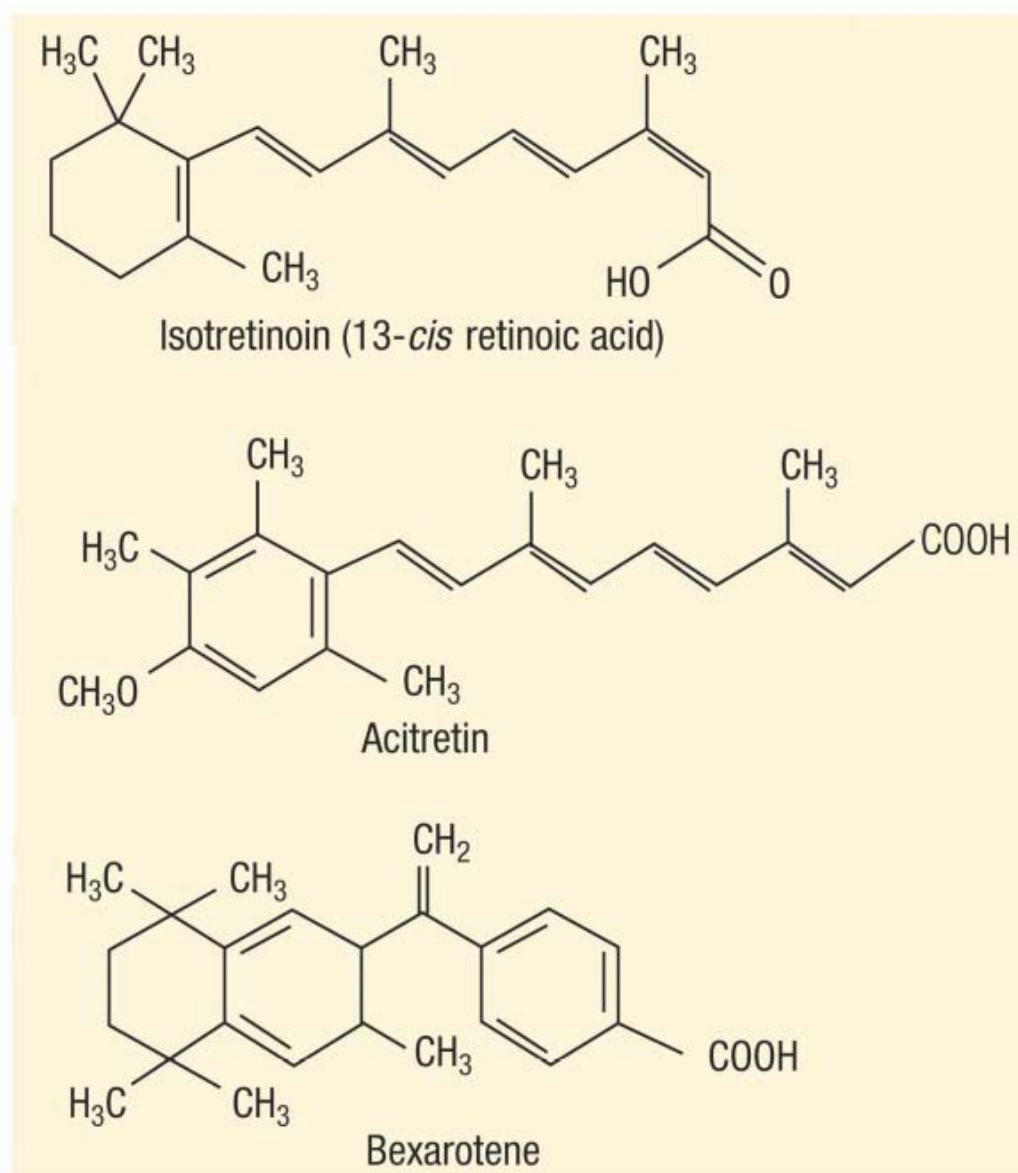


FIGURE 229-1 Chemical structure of three generations of retinoids. Isotretinoin is first generation; in second-generation (e.g., acitretin) the β-ionone ring, is replaced with an aromatic structure. Bexarotene is an example of a third-generation retinoid.

Isotretinoin

Isotretinoin and ATRA are two interconvertible isomers that differ in their elimination half-lives—approximately 20 hours for isotretinoin and 1 hour for ATRA. Isotretinoin undergoes first-pass metabolism in the liver and subsequent enterohepatic recycling. In plasma, isotretinoin is more than 99 percent bound to plasma protein, mainly albumin. It is stored in neither the liver nor adipose tissue, in sharp contrast to vitamin A and etretinate. The major metabolite is 4-oxoisotretinoin, which has reduced bioactivity; both compounds are excreted in urine and feces. After the end of treatment, endogenous concentrations of isotretinoin and its major metabolite are reached within 2 weeks. Therefore, a 1-month post-therapy period

of contraception provides an adequate safety margin.⁷ No clear affinity for any RARs has been identified with isotretinoin.

Acitretin and Etretinate

Etretinate is a prodrug of acitretin that undergoes extensive hydrolysis in the body to yield the corresponding acid metabolite. In animal studies and in clinical studies in patients with severe keratinizing disorders, acitretin is as effective as etretinate.⁸ However, acitretin has a great pharmacokinetic advantage because it is eliminated more rapidly than etretinate.⁹ Etretinate is approximately 50 times more lipophilic than acitretin and binds strongly to plasma lipoproteins, whereas acitretin binds to albumin. This fact has a profound influence on the respective pharmacokinetic properties of the two drugs.

Even when etretinate and acitretin are taken with food, the absorption of the two drugs varies.¹⁰ Etretinate is stored in adipose tissue from which it is released slowly; it has a terminal half-life of up to 120 days. In contrast, acitretin has an elimination half-life of only 2 days.⁹ However, small amounts of etretinate can be formed in patients receiving acitretin if it is taken simultaneously with alcohol.¹¹ This has prompted the manufacturer to extend the time of compulsory contraception in patients taking acitretin to 2 years (3 years in the United States).¹² Acitretin still has a pharmacokinetic advantage over etretinate, however, for all women who strictly avoid alcohol consumption during treatment and for 2 months thereafter.⁹

Acitretin metabolism primarily involves isomerization instead of oxidation. The major metabolite of acitretin is

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its 13-*cis* isomer, which is inactive. Paradoxically, acitretin activates all three RAR sub-types but binds poorly to them.¹³

Bexarotene

Bexarotene is approximately 100-fold more potent in activating retinoid X receptors than RARs. Its absorption is particularly increased by taking it with fatty meals. In plasma, bexarotene is highly bound (more than 99 percent) to proteins that have not yet been characterized, and the ability of bexarotene to displace drugs bound to plasma proteins and the ability of drugs to displace bexarotene is unknown. Bexarotene probably has a clearance profile similar to that of isotretinoin with a terminal half-life of between 7 and 9 hours.¹⁴ Bexarotene is metabolized by CYP 3A4 and generates its own inactive oxidative metabolites via hepatic CYP 3A4 induction. Neither bexarotene nor its metabolites are excreted in urine; elimination is thought to occur primarily via the hepatobiliary system.¹⁵

▪ INDICATIONS

Acne

Isotretinoin is remarkably effective in curing acne, possibly because it affects—primarily or secondarily—all etiologic factors implicated in the pathogenesis of acne: sebum production, comedogenesis, and colonization with *Propionibacterium acnes*.¹⁶ Of all the natural and synthetic retinoids used in humans, only isotretinoin suppresses sebum excretion and reduces sebaceous gland size.

In the early 1980s, isotretinoin treatment was restricted to patients with severe nodulocystic acne. With increasing experience, however, its use has been extended to patients with less severe disease who respond

unsatisfactorily to conventional therapies such as long-term antibiotics because of the increased resistance of *P. acnes* to many antibiotics.^{17,18}

Psoriasis

The retinoid of first choice for oral treatment of psoriasis is acitretin. Acitretin appears to be as effective as etretinate and can be used in the same combination regimens.¹⁹⁻²³ The best results have been obtained in pustular psoriasis of the palmoplantar or generalized (von Zumbusch) type.^{19,24,25} Rebound does not usually occur after treatment is stopped, and reintroduction of the drug when it does occur produces a beneficial response.²⁶ Although complete clearing of plaque-type psoriasis is achieved in only approximately 30 percent of treated patients, significant improvement is obtained in a further 50 percent.^{5,27,28} The decrease in the psoriasis area and severity index is approximately 60 percent to 70 percent, depending on the dosage.^{5,8} Approximately 20 percent of patients may be considered to experience treatment failures. Combination of acitretin with other anti-psoriatic agents may then be required (see Dosing Regimens).

In a 20-week treatment study,²⁹ six of eleven patients (54 percent) with human immunodeficiency virus infection who had psoriasis showed good to excellent responses to acitretin monotherapy (75 mg/day). Both skin and joint manifestations responded to acitretin therapy in most patients. The adverse effects were moderate and well tolerated, and measures of immune parameters did not indicate exacerbation of immunosuppression in most patients.

Isotretinoin has less effect on psoriasis than acitretin or etretinate, although some efficacy has been shown in combination with psoralen plus ultraviolet A light (PUVA) therapy.¹² Nevertheless, some dermatologists use isotretinoin to treat women with psoriasis who need systemic retinoids to avoid the long postacitretin contraception period required.

Cutaneous T-Cell Lymphoma

Some older studies showed that etretinate may induce clinical improvement in patients with CTCL (e.g., mycosis fungoides or Sézary syndrome) with no internal involvement; better results were obtained when etretinate was combined with PUVA treatment or interferon- α therapy. Use of the combination of acitretin or isotretinoin with oral vitamin D₃ (calcitriol) to obtain synergistic effects in the treatment of CTCL has been reported.^{30,31}

In 1999 the FDA approved bexarotene as oral therapy for the treatment of CTCL that is refractory to at least one systemic therapy. In early (IA-IIA) and advanced (IIB-IVB) stages of CTCL (see Chap. 146), oral bexarotene monotherapy produced approximately 60 percent and 50 percent response rates, respectively, at a dosage of 300 mg/m² or more per day within the first 2 months in most patients.^{32,33}

Clinical Uses Not Approved by the U.S. Food and Drug Administration

Multiple other skin disorders respond to retinoids, but for only a few of them is the effect established in controlled studies.³⁴ In many reports the choice of etretinate/acitretin rather than isotretinoin was based not on pharmacologic considerations but on availability of the product. Bexarotene has not been tested extensively for indications other than CTCL.

ICHTHYOSIS

Among the different types of ichthyosis, the best results are obtained with acitretin for non-bullous

congenital ichthyosis such as lamellar ichthyosis. Treatment of bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis) may lead to an initial increase in bullae. Good results also have been achieved in treating recessive X-linked ichthyosis and ichthyosis vulgaris; however, because of its limited severity the disease often does not require retinoid therapy.

DARIER DISEASE

Severe forms of Darier disease (Darier-White disease) are good indications for retinoid therapy. Care should be taken to initiate therapy with a very low dosage, such as 10 mg/day of acitretin, to prevent initial exacerbation of the disease; usually 20 mg/day is sufficient for significant improvement. Long-term treatment is usually needed to prevent relapse. Low-dose isotretinoin therapy has been used especially in women with Darier disease. Combination of retinoids with antibiotics may enhance the clinical effects, because skin lesions are frequently infected.

PITYRIASIS RUBRA PILARIS

Early treatment with retinoids appears to offer the best chance for clearing of pityriasis rubra pilaris. In extensive cases, concomitant use of methotrexate may be advantageous, but this combination carries an increased risk for toxicity. Etretinate is considered to be superior to isotretinoin in the treatment of adult-onset pityriasis rubra pilaris.³⁵

ROSACEA

In severe forms or in treatment-resistant rosacea, isotretinoin therapy may be more effective for inflammatory lesions than for vascular lesions.³⁶ A low daily dose (10 mg) is often sufficient. The best indications are severe cases of rosacea associated with significant seborrhea.

HIDRADENITIS SUPPURATIVA

Isotretinoin has limited effect on hidradenitis suppurativa, but some investigators recommend this therapy during the weeks or months preceding surgical treatment. Prolonged therapy with acitretin/etretinate

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has been used with some success, especially in treating extensive, inflammatory lesions unsuitable for surgery.^{37,38}

PRE-MALIGNANT AND MALIGNANT SKIN LESIONS

Etretinate and acitretin are effective in the treatment of pre-malignant skin lesions, including human papillomavirus-induced tumors and actinic keratoses. In basal cell nevus syndrome and in xeroderma pigmentosum, these drugs reduce dramatically the incidence of malignant degeneration of the skin lesions. A double-blind study demonstrated that acitretin at a dosage of 30 mg/day for 6 months prevented the development of pre-malignant and malignant skin lesions in renal transplant recipients.³⁹

LICHEN SCLEROSUS ET ATROPHICUS

Acitretin/etretinate is an effective treatment for severe lichen sclerosus et atrophicus of the vulva and may be recommended intermittently for patients who are intolerant of or resistant to local therapies.⁴⁰

LUPUS ERYTHEMATOSUS

Both isotretinoin and acitretin have been used successfully in patients with various forms of lupus erythematosus. However, the lesions recur after completion of treatment as quickly as the initial improvement appeared. Acitretin and hydroxychloroquine are equally effective in the treatment of chronic discoid lupus erythematosus and subacute cutaneous lupus erythematosus.¹²

▪ DOSING REGIMENS

Isotretinoin

The initial consensus was that optimal benefit in acne would be achieved with a high daily dose of isotretinoin, approximately 1 mg/kg of body weight per day.¹⁶ This high dose induces undesirable side effects, however, and similar short-term therapeutic results are obtained with a dose below 0.5 mg/kg provided the treatment is maintained over a longer period of time.⁴¹ Empirical data from several centers indicate that post-therapy relapse is minimized by administering a cumulative dose of at least 120 mg/kg,⁴² and no further therapeutic gain is seen beyond approximately 150 mg/kg.¹⁸ This implies 6 to 8 months of therapy. A lag period of 1 to 3 months may occur before the onset of the therapeutic effect. A flare-up of disease during the first few weeks of treatment and the evolution of acne cysts into lesions resembling pyogenic granuloma may be observed.

Continued healing of acne after the discontinuation of therapy regularly occurs. Approximately one-third of patients with acne require a second course of therapy for either persistent disease or relapse. The only factors predictive of resistance to isotretinoin treatment are the presence of closed comedonal acne and of microcystic acne.⁴³

Acitretin and Etretinate

A therapeutic dosage scheme with an initially low dose (10 to 25 mg/day) of acitretin (etretinate requires 20 percent higher dosing because of a higher molecular weight), followed by progressively increasing doses, seems to avoid the increase in the extent of the psoriatic lesions that may occur within a few days of the start of treatment at dosages of 0.5 to 1.0 mg/kg/day (30 to 70 mg/day).¹⁰

Although the efficacy of a dosage of 10 mg/day was not significantly different from that of the placebo in one study,¹⁰ individual patients may respond to dosages as low as 5 mg/day.

Total clearing of the lesions often requires a combination of treatments, such as retinoids plus topical glucocorticoids, topical vitamin D derivatives, dithranol (anthralin), ultraviolet B irradiation, or photochemotherapy (PUVA treatment).⁴⁴⁻⁴⁸

Bexarotene

The recommended initial dosage of bexarotene is 300 mg/m²/day, administered as a single oral dose with meals. Based on the severity of adverse effects, the dosage may be adjusted down to 100 or 200 mg/m²/day or administration may be suspended temporarily. If CTCL does not respond after 8 weeks of therapy, the dosage may be increased to 400 mg/m²/day with careful monitoring.^{32, 33}

▪ INITIATION AND MONITORING OF THERAPY

Isotretinoin

Women with childbearing potential must have a negative result on a pregnancy test and must practice effective contraception during treatment and for 1 month (2 months in some countries) after the completion of therapy.⁴⁹ The SMART (System to Manage Accutane-Related Teratogenicity) and more lately the iPLEDGE program (<http://www.ipledgeprogram.com>) have been put into effect by the FDA and the manufacturer to minimize the risk of isotretinoin teratogenicity. Similar but less strict programs exist in Europe and elsewhere.

Acitretin and Etretinate

Ensuring that the patient avoids pregnancy during therapy is as imperative when prescribing acitretin and etretinate as when prescribing isotretinoin. However, because of the frequent prospect of long-term treatment of more chronic diseases (e.g., psoriasis and ichthyosis) and the slow elimination of aromatic retinoids from the body after interruption of therapy, acitretin (or etretinate) therapy is usually not recommended for female patients with childbearing potential.

Additional precautions before initiating acitretin therapy include measurement of baseline serum lipid and liver enzyme levels, and anamnestic exclusion of skeletal abnormalities. It is also important to inform the patient beforehand about the possibility of increased hair shedding and other mucocutaneous side effects that will appear during therapy.

Monitoring of serum lipid and liver enzyme levels monthly for the first 2 months and then at 2- to 3-month intervals is adequate in patients with normal baseline levels and absence of risk factors (obesity, high alcohol intake, diabetes).

Bexarotene

The recommendations given for the other retinoids should also be followed for bexarotene, and in addition patients who will receive bexarotene should be screened for thyroid disease. Thyroid hormone and lipid levels in blood should be monitored frequently during therapy.

▪ RISKS AND PRECAUTIONS

Teratogenesis is the most serious adverse effect of oral retinoids. The side effects of systemic retinoids qualitatively resemble hypervitaminosis A syndrome, although important differences exist. The acute retinoid toxicities include mucocutaneous lesions (most patients) and abnormal laboratory test results (less common but may be substantial), whereas the chronic retinoid toxicities involve bony changes (rare).

Teratogenic Effects

Retinoid-induced birth defects include auditory, cardiovascular, craniofacial, ocular, axial and acral skeletal, central nervous system (hydrocephalus, microcephaly), and thymus gland abnormalities.⁵⁰

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The putative mechanism is toxic effects on neural crest cells, particularly with exposure during the fourth week of gestation.⁵¹

In men, retinoid therapy does not appear to produce abnormalities in spermatogenesis, sperm morphology, or sperm motility.⁵² However, it is usually recommended that men who are actively trying to father children

avoid systemic retinoid therapy.

Skin and Mucous Membrane Adverse Effects

Most patients receiving retinoids develop dryness of the lips, skin, and mucous membranes. These dose-related effects reflect mainly decreased sebum production, reduced stratum corneum thickness, and altered skin barrier function. Cheilitis is the earliest and the most frequent sign, followed by blepharoconjunctivitis, dry eyes, dry nose, and dry mouth. Xerosis of the skin, associated with pruritus and peeling, especially of the palms and soles, occurs frequently. Skin fragility and fissuring of fingertips sometimes create a problem, especially for those who work with their hands. Photosensitivity is observed especially with isotretinoin and probably reflects the reduction of thickness of the stratum corneum. Bexarotene appears to induce fewer mucocutaneous and ocular side effects than other classes of retinoids; localized or extensive exfoliative dermatitis is the most common cutaneous side effect with bexarotene.¹⁴ *Staphylococcus aureus* colonization tends to correlate with isotretinoin-induced reduction in sebum production and may lead to overt cutaneous infections.⁵³ Various ill-defined skin eruptions, called *retinoid dermatitis*, are observed frequently. The erythema is sometimes difficult to differentiate from an underlying psoriasis or atopic dermatitis.

Ocular Adverse Effects

Blepharoconjunctivitis occurs with varying severity in about one-third of patients treated with isotretinoin and may prevent the use of contact lenses. Bacterial conjunctivitis occurs to a lesser extent than *S. aureus* colonization.⁵⁴ If artificial tears and topical ophthalmologic antibiotic therapy fail to alleviate the conjunctivitis, ophthalmologic consultation should be sought. Alterations in visual function, mainly poor night vision, excessive glare sensitivity, and changes in color perception, also have been reported.⁵⁵

Hair and Nail Adverse Effects

Diffuse or localized hair loss (telogen effluvium), which is more severe during treatment with acitretin than with isotretinoin, is a common complaint, although objective alopecia tends to occur only at higher dosage levels and after several months of therapy. Nail thinning and paronychia-like changes with periungual granulation tissue may occur.

Musculoskeletal Adverse Effects

Skeletal toxicity was first observed in retinoid-treated patients maintained on a high dosage and after an extended period of continuous treatment for disorders of keratinization. Bone pain without objective evidence of any abnormalities and without sequelae is frequent in retinoid-treated patients. Several reports with conflicting results have implicated synthetic retinoids in the formation of diffuse idiopathic skeletal hyperostosis syndrome-like bone changes and in calcification of tendons and ligaments.⁵⁶⁻⁵⁸ Prospective studies have shown that the hyperostotic effects of retinoids are mostly asymptomatic and likely involve worsening of pre-existing skeletal overgrowth rather than de novo changes.^{59,60} Osteoporosis has been observed with hypervitaminosis A and after long-term therapy with etretinate and to a lesser extent isotretinoin.^{61,62} In children, only a few cases of skeletal abnormalities and premature epiphyseal closure⁶³⁻⁶⁵ have been reported. No baseline radiographs are required, although monitoring patients at high risk who receive prolonged high-dose retinoid treatment may be useful.

Muscle pain and cramps rarely occur in patients taking etretinate or acitretin; however, these muscle effects are not infrequent with isotretinoin, particularly in individuals involved in vigorous physical activity

(sometimes accompanied by elevations in creatine phosphokinase levels). Increased muscle tone and axial muscle rigidity and myopathy were reported to be related to etretinate and acitretin therapy.⁶⁶

Central Nervous System and Other Neurologic Adverse Effects

Central nervous system side effects are rare. Although individual signs of increased intracranial pressure such as headache, nausea, and vomiting are observed occasionally, the complete syndrome with papilledema (pseudotumor cerebri) and impaired vision is exceptional.⁶⁷ Concomitant use by isotretinoin-treated patients of tetracyclines, which rarely produce increased intracranial hypertension, is the major risk factor for development of pseudotumor cerebri.

Anecdotal reports suggest a causal association between isotretinoin therapy and severe depression with suicide attempts.⁶⁸ However, large-scale epidemiologic studies provide no evidence that isotretinoin exposure is associated with any greater risk of psychiatric disorders than is antibiotic use in patients with acne.⁶⁹

Pancreatitis

One case of fatal fulminant pancreatitis with acitretin treatment has been reported.⁷⁰ Pancreatitis occurred in three patients treated with oral bexarotene, 300 mg/m² or more per day, in association with marked elevations of fasting serum triglyceride levels.³²

Hypothyroidism

Clinical and biochemical central hypothyroidism occurred in 40 percent of patients in the trials of bexarotene therapy for CTCL. It was rapidly and completely reversible with cessation of therapy without any clinical sequelae.^{32,71}

Renal Adverse Effects

Renal toxicity has not been a characteristic consequence of retinoid administration. Isotretinoin has been administered safely to patients with end-stage kidney disease who were undergoing hemodialysis. However, case reports describing reversible renal function impairment during etretinate therapy advise monitoring of renal function, particularly in patients with a history of renal disorders.⁷²

Inflammatory Bowel Disease

In very rare cases isotretinoin has been linked to exacerbation of inflammatory bowel disease. A 5-year prospective study did not demonstrate an increased risk of inflammatory bowel disease or of cancer, diabetes, or cardiovascular disease in association with long-term etretinate use for psoriasis⁷⁰; similar safety of long-term acitretin or bexarotene therapy has not been established.

Hyperlipidemia

Serum lipid changes are the most frequent abnormalities in laboratory test results

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seen with retinoid therapy. Depending on the type and dosage of retinoid, triglyceride levels are elevated in 50 percent to 80 percent and cholesterol levels in 30 percent to 50 percent of treated patients.^{32,56,73}

Disturbance of blood lipid levels is generally higher with isotretinoin and bexarotene than with acitretin. In

cases of severe retinoid-induced hypertriglyceridemia, eruptive xanthomas and acute pancreatitis may occur. Discontinuation of therapy is required if the triglyceride level reaches 800 mg/dL. A less severe increase may be treated by dosage reduction or reduction in alcohol and tobacco consumption. In some instances, use of lipid-lowering agents may be indicated.⁷⁴ Co-administration of atorvastatin with bexarotene is recommended.¹⁴ Retinoids probably cause hyperlipidemia by increasing the expression of apolipoprotein-C3, which prevents the uptake of lipids from very-low-density lipoproteins into cells.⁷⁵

Liver Toxicity

Transitory abnormal elevations in serum transaminase levels have been reported in approximately 20 percent of patients treated with etretinate or acitretin and occur much less frequently with isotretinoin and bexarotene. Changes in liver function test results usually occur between 2 and 8 weeks after therapy is begun. Transaminase elevations of more than three times the upper normal range should lead to discontinuation of retinoid therapy.

Severe or persistent hepatotoxic reactions occur in fewer than 1 percent of patients. Acitretin therapy elicited no biopsy-proven hepatotoxicity in a 2-year prospective study.⁷⁶ No specific studies have evaluated the use of retinoids in patients with hepatic insufficiency, although this is likely to interfere with drug elimination.

Hematologic Toxicity

A high incidence (28 percent) of dose-related neutropenia has been reported with the use of bexarotene therapy for CTCL, occurring as early as 2 to 4 weeks after initiation of treatment.³² Hematologic abnormalities are much less common with other retinoids. Bleeding complications due to isotretinoin-induced fibrinolysis has been reported.⁷⁷

▪ **COMPLICATIONS**

Most adverse effects associated with retinoids are preventable and manageable with proper patient selection, dosage adjustments, discontinuation of treatment, and routine monitoring for potential toxicity. Absolute contraindications are pregnancy or an attempt to become pregnant, non-adherence to a contraceptive regimen, and breast-feeding. Relative contraindications are leukopenia, alcoholism, elevated cholesterol or triglyceride levels, significant hepatic or renal dysfunction, and hypothyroidism (bexarotene).

The concurrent use of retinoids with other therapies having similar side effects may increase the risk of these adverse events. Tetracyclines (increased intracranial pressure, phototoxicity), alcohol (increased conversion of acitretin to etretinate, hepatotoxicity), methotrexate (hepatotoxicity), and vitamin A supplements (hypervitaminosis A) should be avoided. The concomitant administration of bexarotene and gemfibrozil may result in increased plasma concentrations of bexarotene, at least partially related to CYP 3A4 inhibition by gemfibrozil. In addition, retinoid drug levels may increase with the use of CYP inhibitors such as azoles and macrolides and the CYP competitor cyclosporine, whereas antituberculosis drugs (rifampicin) and anticonvulsants (phenytoin and carbamazepine) actually decrease the drug levels via CYP 3A4 induction.

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