Dapsone and Retinoids

27

David Bacman, Annegret Kuhn, Thomas Ruzicka

Dapsone

Dapsone (4,4'-diaminodiphenylsulphone) has been in clinical use for more than 60 years. It is widely used in the treatment of a variety of infectious diseases, including leprosy and malaria, and it has some action against other parasites. In addition, it has been effective in the treatment of a diversity of cutaneous disorders, particularly those characterized by a neutrophilic infiltrate but also cutaneous manifestations of lupus erythematosus (LE), erythema nodosum, cutaneous vasculitides, pyoderma gangrenosum, bullous dermatoses, and dermatitis herpetiformis (Lang 1979, Mok et al. 1998).

Pharmacology

Chemistry

The chemical structure of dapsone is the simplest of the sulfones, all of which share a characteristic structure: a sulfur atom linking to two carbon atoms. Derivatives of dapsone, such as sulfoxone, are thought to be metabolized to the parent dapsone structure (Fig. 27.1) (Katz 1999, Zhu and Stiller 2001).

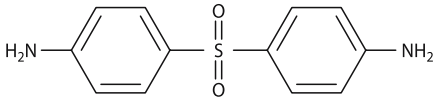
Pharmacokinetics

Absorption

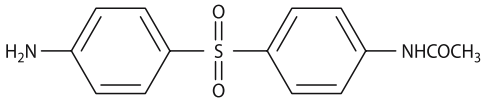
After oral administration, dapsone is well absorbed from the gastrointestinal tract, with a bioavailibility of more than 86%. Peak serum levels are reached 2–6 h after a single dose is administered. After 8–10 days of therapy at a constant dosage level, the serum level stabilizes and remains at that point unless the dosage is changed. The elimination half-life ranges from 12–30 h, which may be due to the enterohepatic circulation of the drug and the extensive protein binding (Katz 1999, Lang 1979, Zhu and Stiller 2001, Zuidema et al. 1986).

Distribution

Dapsone is ca. 70%–90% bound to plasma protein, and its monoacetylated metabolite (monoacetyldapsone [MADDS]) is almost entirely (99%) protein bound. Dapsone seems to be distributed throughout the body, including the skin, liver, kidneys, and erythrocytes. Dapsone crosses the blood-brain barrier and the placenta and is excreted in breast milk. Nevertheless, there are no reports of harmful effects on the fetus in utero, and only a few cases of neonatal hemolysis have been described (Zhu and Stiller 2001, Zuidema et al. 1986).



Dapsone



Monoacetyldapsone

Fig. 27.1. Chemical structure of dapsone and its major metabolite

Metabolism and Excretion

After absorption in the gastrointestinal tract, dapsone is transported to the liver, where it undergoes different metabolic transformations. The two major metabolic pathways involve N-acetylation and N-hydroxylation. Dapsone and its derivatives are acetylated by N-acetyltranferase to the nontoxic metabolites MADDS and diacetyldapsone. As with several other drugs, such as isoniazid and hydralazine, patients show genetic polymorphism in their ability to acetylate dapsone; some patients rapidly acetylate dapsone to MADDS ("rapid" acetylators), whereas in others this process occurs slowly ("slow" acetylators). Deacetylation occurs simultaneously, and a stable equilibrium between MADDS and dapsone is reached within a few hours of oral administration. However, it seems that the rate of acetylation does not relate to the half-life in the body and does not affect the efficacy of the drug. The other major metabolic pathway is hydroxylation, and it is responsible for hematologic side effects, such as methemoglobinemia, hemolysis, and Heinz-body formations. N-Hydroxylation is effected by a variety of cytochrome P-450 enzymes (CYP3A, CYP2E, and CYP2C) forming hydroxylamine, a potentially toxic metabolite, using hepatic microsomes. The levels of expression of these cytochrome P-450 enzymes may be crucial for individual vulnerability to dapsone side effects. Finally, dapsone, MADDS, and hydroxylamine are conjugated in the liver with glucuronic acid in preparation for excretion. Approximately 85%–90% of dapsone is excreted in the urine, primarily as glucuronide. Only 10% is excreted in the bile. Approximately 50% of a single dose of dapsone is excreted within the first 24 h. Probenecid decreases the renal clearance of dapsone, whereas rifampicin increases urinary excretion. Since dapsone is subject to enterohepatic circulation, administration of activated charcoal decreases its elimination half-life by 50% (Katz 1999, Lang 1979, Zhu and Stiller 2001, Zuidema et al. 1989).

Mode of Action

Antibacterial Action

Dapsone acts in leprosy and other infectious diseases in the same way as sulfonamides, inhibiting the synthesis of dihydrofolic acid through competition with para-

aminobenzoate for the active site of dihydropteroate synthetase (Coleman 1993, Wozel and Barth 1988, Zhu and Stiller 2001).

Anti-inflammatory Action

The anti-inflammatory effect of dapsone is not related to its antibacterial effect. Dermatoses that respond to dapsone are in general associated with the accumulation of large numbers of polymorphonuclear leukocytes, mainly neutrophils. After stimulation, neutrophils release the heme-containing enzyme myeloperoxidase, which converts nicotinamide adenine dinucleotide phosphate-dependent oxygen to toxic oxygen intermediates, such as hydrogen peroxide, superoxide anion, hydroxyl radical, hydroxyl ion, and peroxide anion. These intermediates seem to allow microbial killing and to contribute to ongoing tissue injury during inflammation. Dapsone has been shown to protect cells from neutrophil-mediated auto-oxidative tissue injury by converting myeloperoxidase to an inactive compound (compound II), thus suppressing the formation of toxic oxygen intermediates. Dapsone has also been shown to suppress neutrophil chemotactic migration and to interfere with β2 integrin-mediated adherence of neutrophils. Furthermore, it has been suggested that dapsone inhibits the generation of 5-lipoxygenase products in polymorphonuclear leukocytes, lysosomal enzyme activity, and the alternative pathway of complement as well as leukotriene B_4 binding to neutrophils and the neutrophil chemotactic response to leukotriene B_4, thus reducing the inflammatory effect. In addition, it has been reported that dapsone may prevent the generation of prostaglandin D2 in mast cells (Coleman 1993, Lang 1979, Miyachi and Niwa 1982, Ruzicka et al. 1983, Wozel and Barth 1988, Zhu and Stiller 2001).

Indications

Used as an antibiotic, dapsone is effective in the treatment of leprosy and actinomycetoma and in the prophylaxis and treatment of *Pneumocystis carinii* pneumonia. Dapsone has been used in treating many diseases characterized by the abnormal infiltration of neutrophils or eosinophils (Table 27.1).

Dosage

Dapsone given in oral doses of 25–100 mg daily has been reported to be effective in the treatment of annular subacute cutaneous LE (SCLE); urticarial vasculitic lesions complicating systemic LE; the nonscarring form of chronic discoid LE (DLE), today designated as LE tumidus (Fig. 27.2) (Kuhn et al. 2000); bullous eruptions of systemic LE; and oral ulcerations (Coburn and Shuster 1982, Hall et al. 1982, McCormack et al. 1984, Ruzicka and Goerz 1981). In contrast, the response of chronic DLE to dapsone (100–150 mg/day) has been largely disappointing (<30% response rates), especially when lesions are widespread or disseminated (Lindskov and Reymann 1986, Ruzicka and Goerz 1981). Because exacerbation of cutaneous disease occurs when discontinuing therapy, a maintenance dose of 25–50 mg/day is almost always needed (Duna and Cash 1995). Dapsone might be an alternative to antimalarial agents when the latter cause adverse reactions (Lo et al. 1989).

Table 27.1. Indications for dapsone therapy in dermatology (Katz 1999, Lang 1979, Zhu and Stiller 2001)

Erythema elevatum diutinum
Dermatitis herpetiformis
Linear IgA dermatosis
Cicatricial pemphigoid
Bullous pemphigoid
Pemphigus vulgaris
Actinomycetoma
Sneddon-Wilkinson disease (subcorneal pustular dermatosis)
Pyoderma gangrenosum
Sweet syndrome
Eosinophilic cellulitis
Granuloma annulare
Erosive lichen planus
Relapsing polychondritis
Systemic lupus erythematosus
Subacute cutaneous lupus erythematosus
Discoid lupus erythematosus
Bullous lupus erythematosus

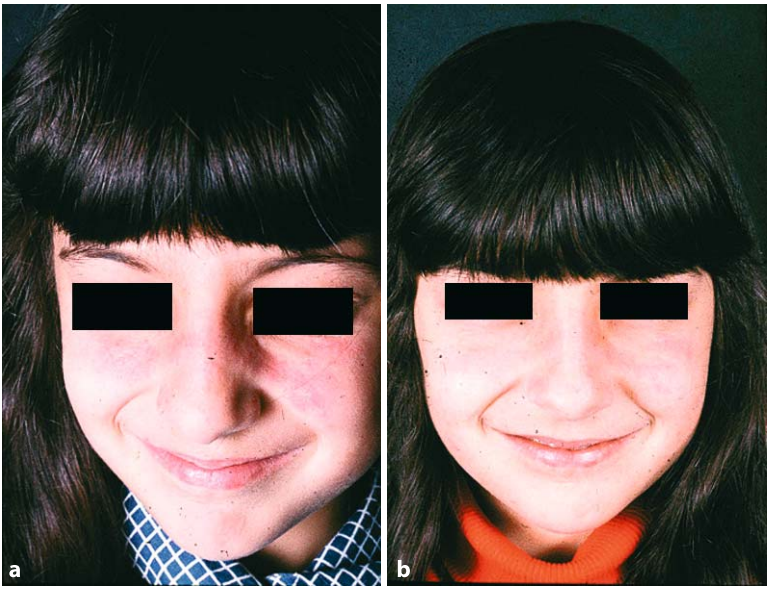


Fig. 27.2. **a** 10-year-old Turkish girl with non-scarring form of discoid lupus erythematosus before therapy. **b** Almost total clearing of skin lesions 3 weeks after therapy with dapsone

Monitoring and Prevention of Side Effects

Before therapy with dapsone is started, a complete blood cell count with differential white count should be obtained. Also, the glucose-6-phosphate dehydrogenase and methemoglobin levels should be tested, since hemolysis and methemoglobinemia are well-known dapsone-dependent side effects. Once therapy has been initiated, the complete blood cell count should be obtained weekly for the first month and then, if stable, every 2 weeks for another 2 months. Thereafter, the complete blood cell count should be done periodically. Serum creatinine and liver enzyme levels should also be measured before therapy starts and should be frequently monitored thereafter (Katz 1999, Lang 1979). To minimize the risk of side effects, the lowest effective dose of dapsone (generally 100 mg/day) should not be exceeded (Duna and Cash 1995, Lo et al. 1989). In addition, concomitant administration of drugs associated with hemolysis and blood dyscrasias, such as sulfonamides, isoniazid, aspirin, ibuprofen, and primaquine, should be avoided (Zhu and Stiller 2001).

Adverse Effects

Hemolysis

Hemolysis with Heinz-body formation is the second most important hematologic side effect of dapsone. Patients treated with 150 mg/day of dapsone will have a significant decrease in the hemoglobin level of almost 2 g/dl. Individuals with glucose-6-dehydrogenase deficiency have an even greater decrease in the hemoglobin level. In vivo and in vitro studies have demonstrated a direct involvement of hydroxylamines in hemolysis. Also, the presence of oxygen-free radicals seems to play a certain role. However, hemolysis does not correlate with the acetylator status of the patient.

Methemoglobinemia

Methemoglobinemia is the most common side effect of dapsone use. In healthy individuals, methemoglobin is constantly produced under physiologic conditions in very low amounts and is reduced by nicotinamide adenine dinucleotide-dependent methemoglobin reductase. After long-term administration of dapsone, more methemoglobin is formed by its hydroxylamine metabolite. Dapsone hydroxylamine reacts with oxyhemoglobin (Fe^{2+}) to form methemoglobin (Fe^{3+}). The methemoglobin level is more evident at the outset of treatment and is dose dependent. Usually, it is well tolerated if the dosage does not exceed 200 mg/day. Individuals with a deficiency of nicotinamide adenine dinucleotide-dependent methemoglobin reductase or with hemoglobinopathy are more susceptible to methemoglobinemia, whereas glucose-6-dehydrogenase-deficient patients are less subject to methemoglobinemia. Symptoms include cyanosis, weakness, tachycardia, dyspnea, dizziness, nausea, headache, and mild jaundice. Dapsone-induced methemoglobinemia can be reduced by coadministration of cimetidine, although this effect seems to vanish after about 3 months, possibly because of cytochrome P-450 enzyme induction (Coleman 1993, Katz 1999, Pfeiffer and Wozel 2003, Zhu and Stiller 2001, Zuidema et al. 1986).

Agranulocytosis

Most cases of agranulocytosis occur within the first 8 to 12 weeks of therapy in 0.2%–0.4% of patients. Although most patients recover, it may be fatal. Agranulocytosis is characterized by a neutrophil count of less than 0.5×10^9/l. The mechanism of dapsone-induced agranulocytosis is unclear. The hydroxylamine metabolite of dapsone is known to be toxic to human bone marrow and to human mononuclear cells in vitro. It is also produced by neutrophils in vitro during the respiratory burst. In addition, red blood cells seem to be involved. When exposed to hydroxylamine, erythrocytes liberate this metabolite and kill mononuclear leukocytes in vitro. Hydroxylamine binds strongly to red blood cells and reaches the bone marrow, where it can damage granulocyte precursors and lead to potentially fatal agranulocytosis (Coleman 1993, Katz 1999, Zhu and Stiller 2001).

Dapsone Hypersensitivity Syndrome

Another uncommon, but severe, adverse side effect is the dapsone or sulphone hypersensitivity syndrome (DHS). The syndrome was first noted by Lowe and colleagues in 1950 and was subsequently termed so by Allday and Barnes. This drug reaction was first noted in patients with lepromatous leprosy, and the incidence of the syndrome has increased in the leprosy population since the introduction of multidrug therapy during the past decades. However, DHS has also been seen in patients with various dermatologic diseases, including LE. It usually occurs during the first 3–5 weeks after the start of therapy and consists of fever, malaise, exfoliative dermatitis, hepatitis, lymphadenopathy, hemolytic anaemia, eosinophilia, leukocytosis, and atypical lymphocytosis. It is an infectious mononucleosis-like picture, although there is no serologic evidence of Epstein-Barr virus, cytomegalovirus, or toxoplasma infection. Age, sex, and initial dose of dapsone did not seem to predict the development of this life-threatening complication. The treatment strategy for DHS is unclear. It includes withdrawal of the drug and institution of systemic corticosteroids. A prolonged course of corticosteroids is needed as dapsone has a long half-life in tissues because of the enterohepatic circulation. The pathogenesis of DHS is unknown. Eosinophilia, corticosteroid response, improvement after drug withdrawal, and occurrence at a wide range of daily dosages from 50 to 300 mg suggest that DHS is an idiosyncratic hypersensitivity reaction to the drug (Mok and Lau 1996, 1998).

Other Side Effects

Neurologic and psychiatric side effects include peripheral neuropathy, depression, and psychosis. Cutaneous manifestations include, among others, erythema multiforme, erythema nodosum, and toxic epidermal necrolysis. Finally, dapsone may have renal (nephritic syndrome and renal papillary necrosis) and hepatic (cholestasis and toxic hepatitis) toxicity (Duna and Cash 1995, Lang 1979, Lo et al. 1989, Zhu and Stiller 2001).

Pregnancy and Lactation

Complications such as neonatal hemolytic disease, neonatal hyperbilirubinemia, and neonatal methemoglobinemia have been reported. However, treatment with dapsone during pregnancy is in general considered to be safe for both mother and fetus. Dapsone crosses the placenta and is excreted in breast milk (Zhu and Stiller 2001).

Retinoids

Retinoids (etretinate, acitretin, and isotretinoin) have revolutionized the treatment of acne, psoriasis, and other disorders of keratinization such as ichthyoses, Darier's disease, and pityriasis rubra pilaris. There is increasing evidence that oral retinoids can also exert effects on various other cutaneous diseases characterized histologically by dermal inflammation. Among these is CLE (Duken 1984, Lo et al. 1989, Windhorst 1982).

Pharmacology

Chemistry

Retinoids are naturally occurring compounds and synthetic derivatives of retinol (vitamin-A alcohol) that show vitamin A activity. There are three generations of synthetic retinoids today. Manipulation of the polar group and the polyene side chain of vitamin A forms the *first generation* of retinoids, which includes tretinoin (all-*trans*-retinoic acid), isotretinoin (13-*cis*-retinoic acid), and alitretinoin (9-*cis*-retinoic acid). The aromatic retinoids, etretinate and acitretin, are produced by replacing the cyclic end group of vitamin A with different substituted and nonsubstituted ring systems and are synthetic retinoids of the *second generation*. The *third-generation* retinoids, tazarotene and adapalene, known as polyaromatic compounds, are topical agents for the treatment of psoriasis and acne (Fig. 27.3). Bexarotene is also a third-generation retinoid and is approved for the systemic treatment of cutaneous T-cell lymphoma (Brecher and Orlow 2003, Orfanos et al. 1987).

Pharmacokinetics

Absorption

The bioavailability of isotretinoin (13-*cis*-retinoic acid) is approximately 25% after oral administration, and it can be increased by food 1.5- to 2-fold. After 30 min, the drug is detectable in the blood, and peak serum levels are reached 1–4 h after oral ingestion. As a result of enterohepatic circulation, secondary and tertiary blood concentration maxima may occur. About 6 h after oral administration, the main metabolite, 4-oxo-isotretinoin, is present in a 2- to 4-fold higher concentration. Isotretinoin and 4-oxo-isotretinoin reach steady-state concentrations within 10 days. The mean elimination half-life of isotretinoin is 19 h and of 4-oxo-isotretinoin is 29 h.

Similar to isotretinoin, the oral absorption of acitretin, the major metabolite of etretinate, is variable. Given with food, the bioavailibility is approximately 60% (range, 36%–95%). Peak serum levels are reached 2 h after a single dose is taken. Plasma concentrations of acitretin and its major metabolite, *cis*-acitretin, reach steady-state within 2–3 weeks. Mean peak concentrations of *cis*-acitretin are considerably higher at steady-state and result from the longer half-life and lower clearance of *cis*-acitretin compared with acitretin. The half-life after multiple doses of acitretin ranges from 3–96 h and of cis-acitretin from 35–148 h (Orfanos et al. 1987, 1997, Wiegand and Chou 1998b).

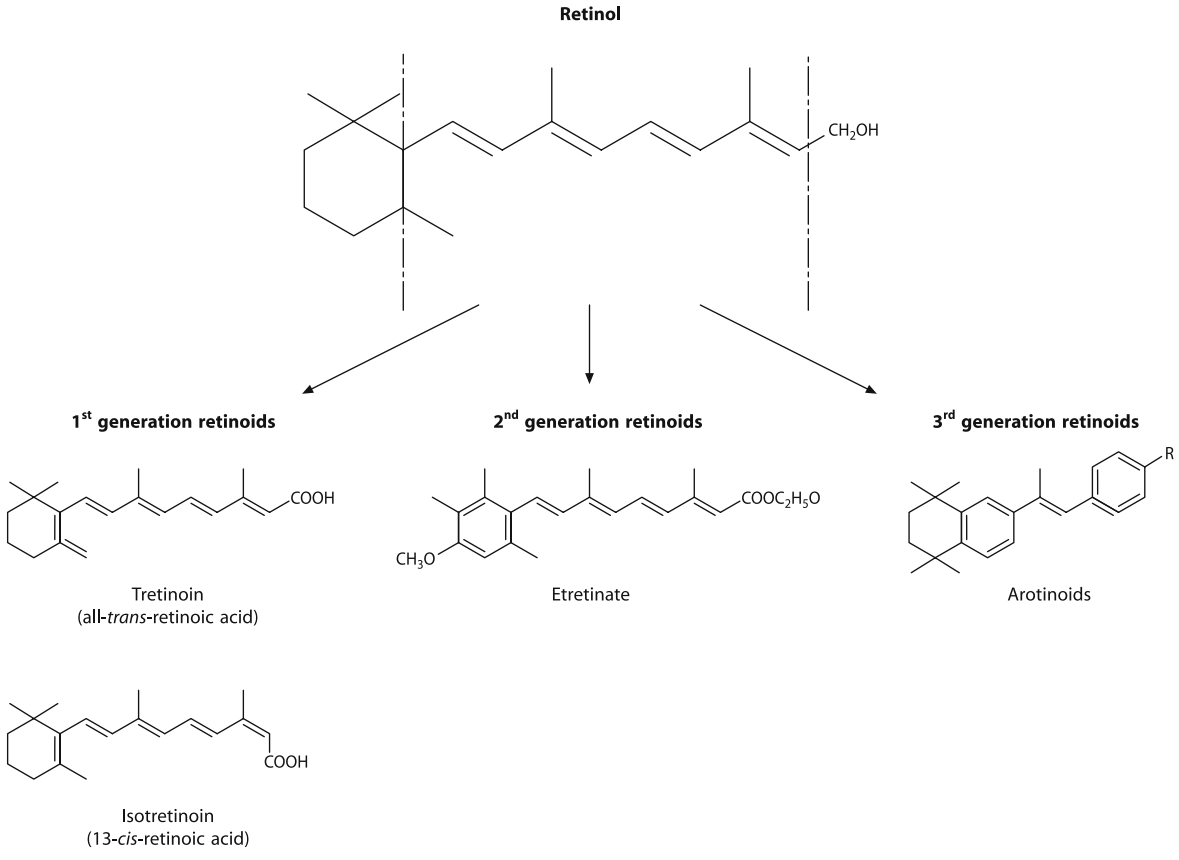


Fig. 27.3. Structural modification of the retinol molecule resulting in three generations of retinoids

Distribution

Isotretinoin is highly lipophilic and is therefore extensively (>99%) bound to plasma proteins, mainly albumin. It has been shown that isotretinoin is not stored in adipose tissue, and there is not specific retention in any organ.

As with isotretinoin, acitretin is to a great extent (98%) bound to plasma proteins, mostly to albumin, caused by its high lipophilicity. Acitretin is not stored in adipose tissue. Isotretinoin and acitretin seem to cross the placenta and to be excreted in breast milk (Orfanos et al. 1987, Wiegand and Chou 1998a).

Metabolism and Excretion

The major metabolites of isotretinoin in the blood following oral administration have been identified as 4-oxo-isotretinoin and 4-hydroxy-isotretinoin, and several glucuronide conjugates are measurable in the bile. In addition, tretinoin, its 4-oxo-metabolite, and 4-hydroxy-retinoic acid have also been detected. Approximately 20%–30% of isotretinoin isomerizes to tretinoin and is metabolized by this route. Excretion of isotretinoin occurs after conjugation with the feces or after metabolism with urine. Acitretin is metabolized into at least four compounds, the major metabolite being 13-*cis*-acitretin (Fig. 27.3). Because of their polar carboxylic acid group, both compounds are less lipophilic than etretinate and therefore do not accumulate in adipose tissue and are eliminated more rapidly in feces and urine. However, it is known that acitretin is in part converted into etretinate and that subsequently etretinate is stored in adipose tissue. It has been reported that the consumption of alcohol stimulates the formation of etretinate from acitretin, but it is not a necessary precondition for back-metabolization (Allen and Bloxham 1989, Lucek and Colburn 1985, Orfanos et al. 1997, Wiegand and Chou 1998b).

Mode of Action

The mode of action of the retinoids has not been completely elucidated, but they have profound effects on differentiation, cell growth, and immune response. Retinoids are capable of regulating epithelial differentiation in the skin, mucous membranes, and mesenchymal tissues. They promote cell proliferation in normal epidermis but inhibit epidermal keratinocytes in psoriatic lesions. Sebaceous glands are significantly reduced in size (up to 90%), and sebum excretion is reduced by isotretinoin. In general, retinoids are reported to stimulate humeral and cellular immunity, although immune-inhibitory effects have also been described. They can boost antibody production, increasing T-helper cells but not natural killer cells. Anti-inflammatory effects include inhibition of motility of neutrophils and eosinophils and their migration into the dermis. Isotretinoin seems to inhibit nitric oxide and tumor necrosis factor α production by keratinocytes and to reduce inducible nitric oxide synthase messenger RNA levels. The discovery of specific cellular binding proteins and nuclear receptors for retinoids has deeply advanced our understanding of the diverse biological processes of retinoids. These observations have also highlighted the complexity of interactions between retinoids and other hormonal signaling molecules. There are two groups of cellular binding proteins, the cellular retinol binding proteins (CRBP I and II) and the cellular retinoic acid binding proteins (CRABP I and II). CRABP II is the predominant form in human skin, although CRABP I is also present at low levels.

Expression of CRABP II is up-regulated by topical application of retinoic acid. CRABP II serves as an early marker for retinoic action in the skin and may regulate the bioavailability of retinoids by reducing the free levels available to reach the nucleus. Cellular retinoic acid binding proteins act as transporters across cell membranes and mediate transfer to the nucleus. In the nucleus of the target cell, retinoid molecules bind to their nuclear receptors. Two main classes of nuclear retinoid receptors have been identified, retinoic acid receptors (RARs) and retinoid X receptors (RXRs), each composed of α, β, and γ subtypes. In addition, there is more than one isoform of each receptor subtype. RARγ and RXRα are expressed predominantly in the skin. RARs can bind both all-*trans*-retinoic acid and 9-*cis*-retinoic acid, whereas RXRs interact with 9-*cis*-retinoic acid. In contrast, 13-*cis*-retinoic acid shows low affinity for RARs. The nuclear receptors combine, with the attached retinoid molecules, to form homodimers (RAR/RAR, RXR/RXR) or heterodimers (RAR/RXR) and then subsequently bind to stretches of DNA known as response elements. As a result, gene transcription of the target gene is stimulated and the production of proteins, which may directly mediate the effects of the retinoid, is activated (Allen and Bloxham 1989, Craven and Griffiths 1996, Orfanos et al. 1987, 1997).

Indications and Dosage

The efficacy of systemic retinoid therapy in a variety of dermatologic diseases, such as acne, psoriasis (pustular and erythrodermic types), and disorders of keratinization (ichthyoses, symmetric progressive erythrokeratoderma, Darier disease, pityriasis rubra pilaris, and palmoplantar hyperkeratosis), is well known. There are also reports of successful treatment of other dermatologic conditions, including disorders of epidermal differentiation (epidermodysplasia verruciformis, confluent and reticulated papillomatosis, and axillar granular parakeratosis) and inflammatory and immunodermatoses (atrophoderma vermiculatum, lichen planus, sarcoidosis, and granuloma annulare). Various synthetic retinoids have also been tried in the treatment of patients with different forms of cutaneous LE (CLE), and there are numerous reports of good responses to etretinate, acitretin, and isotretinoin (Duna and Cash 1995, Furner 1990b). Etretinate has been shown to be effective in the treatment of DLE, particularly the hyperkeratotic variant, and SCLE (Grupper and Berretti 1984, Lubach and Wagner 1984, Ruzicka et al. 1985). Subsequently, acitretin, the major metabolite of etretinate, given in oral doses of 50 mg/day initially, has also been reported to be effective in patients with DLE and SCLE (Fig. 27.4). The dose was individually adjusted according to clinical efficiency and side effects. The main advantage of using acitretin in the treatment of CLE compared with etretinate is the much shorter elimination half-life of the drug (although there is retroconversion to etretinate in some patients). The interesting observation that hydroxychloroquine leads to a decrease in serum triglyceride levels suggests that this effect may offset the acitretin-induced hypertriglyceridemia, a side effect frequently limiting the use of this drug. Therefore, the combination of low doses of acitretin with hydroxychloroquine should be considered (Ruzicka et al. 1988, 1992). Finally, there are also reports describing therapeutic responses of LE to isotretinoin. Isotretinoin given in doses from 0.5 to 1.0 mg/kg per day showed clinical improvement in patients with DLE and SCLE, particularly in those with erythematous, scaly lesions. The therapy was associ-

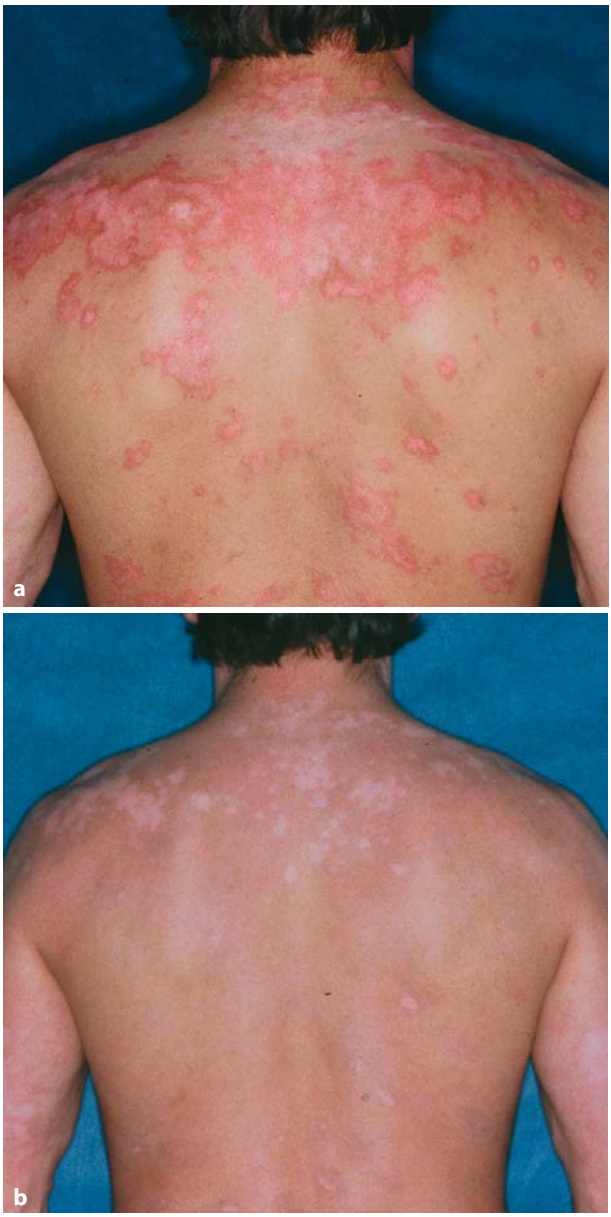


Fig. 27.4. **a** 29-year-old patient with subacute cutaneous lupus erythematosus before therapy. **b** Complete clearing of skin lesions with extensive depigmentation two weeks after therapy with acitretin

ated with the resolution of cutaneous histopathologic abnormalities, conversion of abnormal lesional direct immunofluorescence to normal, normalization of the epidermis on electron microscopy, and reduction in the number of T cells near the dermoepidermal junction without change in the ratio of T-helper (inducer) cells to T-suppressor (cytotoxic) cells. Retinoids may be useful in establishing rapid control of resistant lesions or in treating intermittent acute flare-ups, whether used as monotherapy or in combination with antimalarials or corticosteroids and in patients with CLE refractory to other drug regimens. Because of the recurrence of skin lesions after discontinuing medication use, long-term treatment may be needed to maintain control (Brecher and Orlow 2003, Duna and Cash 1995, Ellis and Krach 2001, Furner 1990a, Newton et al. 1986, Shornik et al. 1991).

Contraindications

Pregnancy, lactation, and severe hepatic and renal dysfunction (persistent elevated liver enzyme, urea, and creatinine levels) are absolute contraindications for oral retinoid treatment (Orfanos et al. 1987).

Monitoring and Prevention of Side Effects

Laboratory examinations of liver function (transaminases and γ-glutamyl transferase), alkaline phosphatase, serum lipids, and renal function tests (creatinine) should be performed before treatment is started, 3–4 weeks thereafter, and then at 3-month intervals. Patients with diabetes mellitus, obese patients, and alcoholic patients are at increased risk for hepatotoxicity and require more frequent liver function testing during therapy with retinoids. Concomitant use of other drugs (β-blockers, hormonal corticosteroid contraceptives, and thiazide diuretics) with an additive effect on lipid levels should be performed carefully. Other therapeutic agents that may interact with retinoids, such as antidiabetics (alterations in blood glucose), corticosteroids and tetracyclines (hyperlipidemia and pseudotumor cerebri), and methotrexate (hepatotoxicity), should be monitored cautiously or avoided. Supplementary therapy with vitamin A should be avoided while taking retinoids. To minimize skeletal toxicity, the lowest possible dosage in patients receiving long-term retinoid therapy should be used. Baseline radiography may be useful to document pretreatment bone status in addition to control x-rays once a year for individuals requiring prolonged treatment (Brecher and Orlow 2003, Katz et al. 1999, Orfanos et al. 1987).

Adverse Effects

The most common side effects are generally mucocutaneous and seem to be dose related. Many of these side effects are similar to the clinical findings in vitamin A intoxication but are less severe (Ellis and Krach 2001, Peck and DiGiovanna 1999).

Mucocutaneous

Acute mucocutaneous toxicity is a frequently observed side effect of retinoid use. Most of these symptoms are well tolerated, dose dependent, treatable, and reversible when treatment is discontinued or the dosage is reduced. Cheilitis and dry nasal

mucosa are the most common manifestations, and they occur in almost all patients receiving isotretinoin in sufficient dosage. Actually, the complete absence of these symptoms when associated with failure of drug response should raise the suspicion of noncompliance. Cheilitis generally responds to continual application of topical emollients during therapy. Lubrication to the anterior nares is also often required to alleviate dry nasal mucosa, which may cause nosebleeds in some patients. Xerosis cutis occurs in approximately 80% of patients and is often associated with pruritus. It has been suggested that tolerance of symptoms may develop during treatment. Photosensitivity affects approximately 10% of patients. Isotretinoin seems to stimulate granulation tissue, which can occasionally lead to pyogenic granuloma-like eruptions in sites of minor trauma and within acute lesions. Etretinate and acitretin show comparable mucocutaneous side effects. Although diffuse thinning of the hair and increased brittleness of the nails may occur during isotretinoin therapy, it is more common with administration of acitretin (Brecher and Orlow 2003, Ellis and Krach 2001, Peck and DiGiovanna 1999).

Ophthalmologic

Xerophthalmia occurs in one third of patients during isotretinoin therapy and is caused by decreased meibomian gland secretion, leading to an altered composition of the tear film and shortening of the tear film break-up time. This may lead to blepharoconjunctivitis, exposure keratitis, and corneal ulceration in extreme cases. Some patients may also develop a contact lens intolerance. Application of artificial tears several times a day can help alleviate these symptoms. Other ophthalmologic toxicities from retinoids include corneal opacities, decreased night vision (as a result of interference with steps in the rhodopsin cycle), transient acute myopia, papilledema, and cataracts. Rarely, dry eye syndrome and decreased night vision have been reported to persist after discontinuation of therapy. Etretinate and acitretin use have been shown to cause many of the same ocular side effects as isotretinoin therapy. However, isotretinoin seems to have a greater ability to suppress meibomian gland secretion (Brecher and Orlow 2003, Ellis and Krach 2001, Katz et al. 1999, Orfanos et al. 1987, Peck and DiGiovanna 1999).

Teratogenicity

Retinoids are known to be teratogenic and can lead to fetal abnormalities. The birth defects characteristically induced by retinoids, so-called retinoic acid embryopathy, include central nervous system abnormalities (hydrocephalus and microcephaly), external ear abnormalities (anotia and small or absent external auditory canals), cardiovascular abnormalities (septal wall and aortic defects), facial dysmorphia, eye abnormalities (microphthalmia), thymus gland and bone abnormalities. In addition, premature births, parathyroid hormone deficiency, and cases of low IQ in the absence of other central system abnormalities have been reported. Retinoid effects on neural crest cells during the fourth week after fertilization may be responsible for many of the observed malformations. Serum levels of the β subunit of human chorionic gonadotropin should be checked before therapy, and effective contraception is mandatory during and after treatment. Isotretinoin has a short half-life, and, therefore, contraceptive measures need to be taken for only 1 month after cessation of treatment. Etretinate and acitretin both have a long half-life. Although acitretin has a

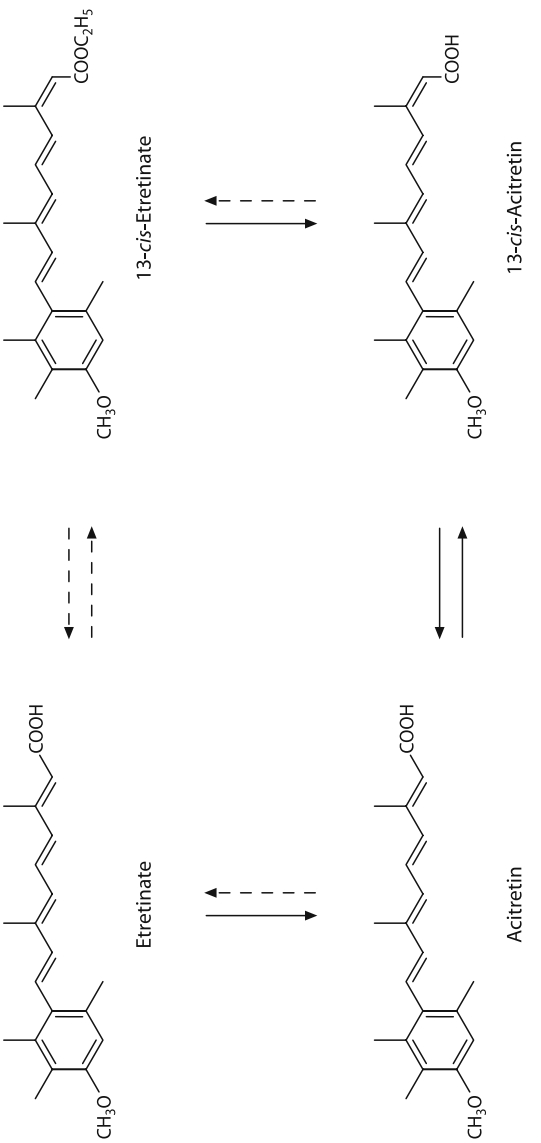


Fig. 27.5. Chemical structures of acitretin and etretinate and their major metabolites

much shorter half-life than etretinate, it is recommended that pregnancy should not occur for at least 3 years after the cessation of acitretin therapy, since some patients back-metabolize acitretin to etretinate (Fig. 27.5). Males can safely father children even when they are taking the drug (Brecher and Orlow 2003, Duna and Cash1995, Lo et al. 1989).

Skeletal Involvement

Administration of retinoids induces bone toxicities similar to those of chronic hypervitaminosis A (remodeling of long bones, cortical hyperostosis, decalcification, premature epiphyseal closure, periosteal thickening, and osteoporosis). In general, synthetic retinoids produce bony changes such as diffuse idiopathic skeletal hyperostosis, including anterior spinal ligament calcification, osteophytes, and bony bridges, but without narrowing of the disk space. Calcification of the anterior spinal ligament with bony bridging of vertebrae has been observed with long-term, high-dose (2 mg/kg per day) isotretinoin therapy, and minimal spinal hyperostosis has been reported in 10% of patients treated with short-term, low-dose isotretinoin. Ossification of the spinal posterior longitudinal ligament is rare. Extraspinal involvement (extraspinal tendon and ligament calcification) is significantly increased in patients receiving long-term etretinate therapy at an average dose of 0.8 mg/kg per day. Premature epiphyseal closure resulting in retardation of growth has been rarely described in children with oral retinoid treatment. The incidence of decreased bone mineral density is still under investigation. No changes in bone mineralization or in markers of bone turnover have been found after short-term therapy with isotretinoin. However, osteoporosis has been identified in patients who received long-term etretinate therapy (Brecher and Orlow 2003, Orfanos et al. 1987, Peck and DiGiovanna 1999).

Neuromuscular Involvement

Headache, fatigue, and lethargy may rarely occur during isotretinoin therapy. However, if headaches become persistent and are associated with nausea, vomiting, and visual changes, the drug should be discontinued immediately and pseudotumor cerebri should be excluded. Since tetracycline, doxycycline, and minocycline may increase the risk of intracranial hypertension, the concomitant use of these drugs and isotretinoin should be avoided. There is a single case report of pseudotumor cerebri in an adult patient receiving acitretin without concomitant antibiotic treatment. Myalgias, sometimes associated with elevated creatinine phosphokinase levels, occur in up to 15% of patients taking isotretinoin, particularly in physically active patients. It has been reported that the elevated creatinine phosphokinase levels return to normal within 2–4 weeks. In general, arthralgias are rarely seen in patients treated with retinoids, and they disappear after discontinuation of therapy. However, arthralgias and back pain in adolescents taking isotretinoin have been observed, although the cause of the back pain is unknown (Brecher and Orlow 2003, Ellis and Krach 2001, Peck and DiGiovanna 1999).

Gastrointestinal Involvement

Retinoids may alter liver function tests, most commonly the transaminases but also other tests (alkaline phosphatase, lactic dehydrogenase, and bilirubin). Elevations of transaminase levels occur in approximately 15% of patients, but they generally return

to normal within 2–4 weeks, even when therapy is continued. Severe hepatotoxic reactions resulting from retinoid use are rare and idiosyncratic. However, a correlation between long-term retinoid therapy and chronic liver toxicity has not been demonstrated. Nonspecific gastrointestinal side effects, such as nausea, diarrhea, and abdominal pain, have been reported with isotretinoin therapy but are infrequent. Although the oral administration of isotretinoin has been linked with inflammatory bowel disease flare-up, a causal relationship has not been established. In fact, isotretinoin has been given to patients with known Crohn's disease and ulcerative colitis without complications (Brecher and Orlow 2003, Ellis and Krach 2001, Katz et al. 1999, Peck and DiGiovanna 1999).

Lipid Involvement

Retinoid therapy may cause hyperlipidemia, probably due to both increased synthesis and decreased elimination of blood lipids. An elevation in serum triglyceride levels in excess of 800 mg/dl has been reported in approximately 25% of patients, a decrease in high-density lipoprotein levels has been shown in approximately 15% of patients, and an increase in cholesterol levels has been shown in approximately 7% of patients receiving isotretinoin therapy. Lipid levels normalize in most patients by reducing the daily retinoid dose, by introducing a diet low in fat and carbohydrates, or by administering lipid-lowering medication. Cessation of treatment should be considered only if abnormal lipid values persist for a long period. In cases of severe hypertriglyceridemia (triglyceride level >1000 mg/dl), patients are at risk for eruptive xanthomata and acute pancreatitis. Hypertriglyceridemia has also been observed during therapy with etretinate and acitretin. Increased serum lipid levels are of particular concern in patients with risk factors such as obesity, high alcohol intake, diabetes mellitus, and pretreatment hypertriglyceridemia (Brecher and Orlow 2003, Katz et al. 1999, Orfanos et al. 1987, Peck and DiGiovanna 1999).

Renal Involvement

Renal toxicity is not a characteristic effect of retinoid therapy. Isotretinoin can be safely administered to patients with end-stage kidney disease who undergo hemodialysis (Ellis and Krach 2001, Peck and DiGiovanna 1999).

Psychological Involvement

Psychiatric disorders such as depression, irritability, psychosis, attempted suicide, and actual suicide have been reported in individuals during and after isotretinoin therapy. However, there is no evidence that the use of isotretinoin is associated with an increased risk for depression or suicide. Psychiatric evaluation and treatment may still be needed (Brecher and Orlow 2003, Ellis and Krach 2001).

In conclusion, dapsone and retinoids may be useful alternatives in the treatment of resistant skin lesions and in patients with CLE refractory to other therapeutic regimens, given as monotherapy or in combination with antimalarials or corticosteroids, considering the indication and the possible side effects.

References

Allen JG, Bloxham DP (1989) The pharmacology and pharmacokinetics of the retinoids. Pharmacol Ther 40:1–27

Brecher AR, Orlow SJ (2003) Oral retinoid therapy for dermatologic conditions in children and adolescents. J Am Acad Dermatol. 49:171–182

Callen JP (1990) Treatment of cutaneous lesions in patients with lupus erythematosus. Dermatol Clin 8:355–365

Coburn PR, Shuster S (1982) Dapsone and discoid lupus erythematosus. Br J Dermatol 106:105–106

Coleman MD (1993) Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. Br J Dermatol 129:507–513

Craven NM, Griffiths CE (1996) Topical retinoids and cutaneous biology. Clin Exp Dermatol 21:1–10

Duna GF, Cash JM (1995) Treatment of refractory cutaneous lupus erythematosus. Rheum Dis Clin North Am 21:99–115

Duken CM (1984) Retinoids: a review. J Am Acad Dermatol 11:541–552

Ellis CN, Krach KJ (2001) Uses and complications of isotretinoin therapy. J Am Acad Dermatol 45:S150–157

Furner BB (1990a) Treatment of subacute cutaneous lupus erythematosus. Int J Dermatol 29:542–547

Furner BB (1990b) Subacute cutaneous lupus erythematosus response to isotretinoin. Int J Dermatol 29:587–590

Grupper C, Berretti B (1984) Lupus erythematosus and etretinate. In: Cunliffe WJ, Miller AJ (eds) Retinoid therapy. MTP, Lancaster, pp 73–82

Hall RP, Lawley TJ, Smith HR, Katz SI (1982) Bullous eruption of systemic lupus erythematosus. Ann Intern Med 97:165–170

Katz SI (1999) Sulfones. In: Freeberg MI, Eisen ZA, Wolff K, Austen FK, Goldsmith AL, Katz IS, Fitzpatrick BT (eds) Dermatology in general medicine, 5th ed. McGraw-Hill, New York, pp 2790–2794

Katz HI, Waalen J, Leach EE (1999) Acitretin in psoriasis: an overview of adverse effects. J Am Acad Dermatol 41:S7–S12

Kuhn A, Richter-Hintz D, Oslislo C, Ruzicka T, Megahed M, Lehmann P (2000) Lupus erythematosus tumidus – a neglected subset of cutaneous lupus erythematosus: report of 40 cases. Arch Dermatol 136:1033–1041

Lang PG Jr (1979) Sulfones and sulfonamides in dermatology today. J Am Acad Dermatol 1:479–492

Lindskov R, Reymann F (1986) Dapsone in the treatment of cutaneous lupus erythematosus. Dermatologica 172:214–217

Lo JS, Berg RE, Tomecki KJ (1989) Treatment of discoid lupus erythematosus. Int J Dermatol 28:497–507

Lubach D, Wagner G (1984) Erfolgreiche Behandlung eines subakut kutanen Lupus erythematodes mit Etretinat. Aktuel Dermatol 10:142–144

Lucek RW, Colburn WA (1989) Clinical pharmacokinetics of the retinoids. Clin Pharmacokinet 10:38–62

McCormack LS, Elgart ML, Turner ML (1984) Annular subacute cutaneous lupus erythematosus responsive to dapsone. J Am Acad Dermatol 11:397–401

Miyachi Y, Niwa Y (1982) Effects of KI, colchicine and dapsone on the generation of PMNL-derived oxygen intermediates. Br J Dermatol 107:209–214

Mok CC, Lau CS (1996) Dapsone syndrome in cutaneous lupus erythematosus. J Rheumatol 23:766–768

Mok CC, Lau CS, Wong RW (1998) Toxicities of dapsone in the treatment of cutaneous manifestations of rheumatic diseases. J Rheumatol 25:1246–1247

Newton RC, Jorizzo JL, Solomon AR Jr, Sanchez RL, Daniels JC, Bell JD, Cavallo T (1986) Mechanism-oriented assessment of isotretinoin in chronic or subacute cutaneous lupus erythematosus. Arch Dermatol 122:170–176
Orfanos CE, Ehlert R, Gollnick H (1987) The retinoids. A review of their clinical pharmacology and therapeutic use. Drugs 34:459–503
Orfanos CE, Zouboulis CC, Almond-Roesler B, Geilen CC (1997) Current use and future potential role of retinoids in dermatology. Drugs 53:358–388
Peck GL, DiGiovanna JJ (1999) Retinoids. In: Freeberg MI, Eisen ZA, Wolff K, Austen FK, Goldsmith AL, Katz IS, Fitzpatrick BT (eds) Dermatology in general medicine. 5th ed. McGraw-Hill, New York, pp 2810–2821
Pfeiffer C, Wozel G (2003) Dapsone and sulfones in dermatology: overview and update. J Am Acad Dermatol 48:308–309
Ruzicka T, Goerz G (1981) Dapsone in the treatment of lupus erythematosus. Br J Dermatol 104:53–56
Ruzicka T, Wasserman SI, Soter NA, Printz MP (1983) Inhibition of rat mast cell arachidonic acid cyclooxygenase by dapsone. J Allergy Clin Immunol 72:365–370
Ruzicka T, Meurer M, Braun-Falco O (1985) Treatment of cutaneous lupus erythematosus with etretinate. Acta Derm Venereol 65:324–329
Ruzicka T, Meurer M, Bieber T (1988) Efficiency of acitretin in the treatment of cutaneous lupus erythematosus. Arch Dermatol 124:897–902
Ruzicka T, Sommerburg C, Goerz G, Kind P, Mensing H (1992) Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. Br J Dermatol 127:513–518
Shornick JK, Formica N, Parke AL (1991) Isotretinoin for refractory lupus erythematosus. J Am Acad Dermatol 24:49–52
Wiegand UW, Chou RC (1998) Pharmacokinetics of oral isotretinoin. J Am Acad Dermatol 39:S8–12
Wiegand UW, Chou RC (1998) Pharmacokinetics of acitretin and etretinate. J Am Acad Dermatol 39:S25–33
Windhorst DB (1982) The use of isotretinoin in disorders of keratinisation. J Am Acad Dermatol 6:708–709
Wozel G, Barth J (1988) Current aspects of modes of action of dapsone. Int J Dermatol 27:547–552
Zhu YI, Stiller MJ (2001) Dapsone and sulfones in dermatology: overview and update. J Am Acad Dermatol 45:420–434
Zuidema J, Hilbers-Modderman ES, Merkus FW (1986) Clinical pharmacokinetics of dapsone. Clin Pharmacokinet 11:299–315