Retinoids and Phototherapy for Psoriasis

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ABSTRACT. Retinoids are the most widely used agents for systemic treatment of psoriasis; as structural and functional analogs of vitamin A, they are involved in the regulation of several biologic functions. Acitretin is the oral retinoid currently used, alone or in combination with other treatments, for plaque type, erythrodermic, and pustular psoriasis. Due to its high teratogenic effect, therapeutic contraception is required for women taking the drug. Narrowband ultraviolet B (nbUVB, 311 ± 2 nm) is effective for guttate and plaque-type psoriasis. At the molecular level, UV light acts (1) directly (type I reaction) inducing the formation of pyrimidine dimers that, in turn, cause a transient cellular growth arrest; and (2) indirectly (type II reaction) through the generation of reactive oxygen species that act on key molecules such as lipids (in particular lipid membranes), proteins, and nucleic acids. Several studies show that UV rays can cause a transient decrease in DNA, RNA, and protein synthesis. These events are accompanied by a temporary normalization of cell kinetics of psoriatic keratinocytes. Phototherapy is carried out 3 times a week alone or in combination with topical treatments and/or acitretin. Several studies have confirmed that oral retinoids together with nbUVB (ReUVB) reduce the recovery time and also the doses of both acitretin and nbUVB. The regimen is carried out treating the patient with acitretin alone (0.5 mg/kg bw) for 2 weeks, then the dose of acitretin is reduced to 0.3 mg/kg bw, and the nbUVB is added 3 times a week until complete resolution of disease. As retinoids exert an anticarcinogenic effect, the ReUVB regimen could lower skin cancer risk resulting from longterm UVB therapy. (J Rheumatol 2009;36 Suppl 83:71-72; doi:10.3899/jrheum.090231)

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ORAL RETINOIDS

Retinoids, in particular etretinate and acitretin, are the most widely used agents for systemic treatment of psoriasis[1]. As structural and functional analogs of vitamin A, they are involved in the regulation of several biologic functions (Table 1) after being transported to the nucleus by intracellular carriers, unwinding their effects on DNA transcription through binding to 2 distinct families of nuclear receptors: RAR (retinoic acid receptors) and RXR (retinoid X receptor). The mechanism of retinoid action in many dermatologic conditions is still unknown and the nuclear receptor concept does not satisfactorily explain the biological diversity of retinoid effects[2]. Both etretinate and acitretin, monoaromatic second generation retinoids, act on psoriasis by not only inducing normalization of differentiation and proliferation of keratinocytes but also modifying the inflammatory response and neutrophil function[2]. The oral bioavailability of retinoids is enhanced when administered with food due to their lipophilic properties, and metabolism occurs mainly in the liver[2].

Acitretin is the major metabolite of etretinate and, even though they are equally effective, the former is currently used for its short half-life (2 days) compared with the longer half-life of etretinate (120 days). This is important, taking into account that systemic retinoids, potent teratogens, can provoke embryopathy including abnormalities of the central nervous system, ear, cardiovascular system, and axial and acral skeleton, as well as craniofacial and thymus gland anomalies[3]. Health authorities advise a therapeutic contraceptive period of at least 3 years for women taking oral retinoids. Concurrent use of acitretin and alcohol must be avoided because it induces the back conversion of acitretin to etretinate, thus prolonging the risk of side effect. Relative contraindications for acitretin are liver and severe kidney dysfunction, hyperlipemia, young children, and pseudotumor cerebri. Dose-dependent mucocutaneous toxicity is the most commonly observed side effect with oral retinoids. Decreased production of sebum, reduced stratum corneum thickness, and altered skin barrier function may produce dry lips or cheilitis after starting therapy. Dryness and fragility of the nasal mucosa leading to epistaxis are also frequently observed, as xerophthalmia may be a contraindication for the use

Table 1. Biologic effects of retinoids.

- Modulation of proliferation and differentiation
- Antikeratinization
- Alteration of cellular cohesiveness
- Immunologic and antiinflammatory effects
- Inhibition of tumor promotion and malignant cell growth
- Induction of apoptosis
- Effects on extracellular matrix components

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of contact lenses. Diffuse or localized hair loss (telogen effluvium) is a common complaint at high dosage levels. Use of tetracycline and minocycline, during retinoid therapy, may increase intracranial pressure. Vitamin A supplements may lead to hypervitaminosis, and simultaneous use of methotrexate can increase the liver toxicity[4]. Acitretin is indicated for plaque-type psoriasis, which responds to a dosage of 0.5 mg/kg/day. Several trials have shown the efficacy of acitretin in monotherapy for erythrodermic, plaque-type, and pustular psoriasis[5,6]. Total clearance of psoriatic lesions usually requires a combination of therapies such as topical treatments or phototherapy[7].

PHOTOTHERAPY

Many psoriatic patients improve after multiple sun exposures. The effectiveness of the solar spectrum is in the short ultraviolet range (UVB = 290–320 nm); the most effective wavelength for clearing psoriasis lies around 313 nm[8]. Accordingly, narrowband UVB (nbUVB) sources, emitting 311 ± 2 nm, have been developed in the last 20 years. Studies comparing the efficacy of nbUVB phototherapy versus PUVA photochemotherapy (oral psoralens followed by ultraviolet A radiation, 320–400 nm) demonstrate that these 2 modalities are equally effective[9]. At the molecular level, UV light acts (1) directly (type I reaction) inducing the formation of pyrimidine dimers that, in turn, cause a transient cellular growth arrest; and (2) indirectly (type II reaction) through the generation of reactive oxygen species that act on key molecules such as lipids (in particular lipid membranes), proteins, and nucleic acids[10]. Several studies show that UV rays can cause a transient decrease in DNA, RNA, and protein synthesis. These events are accompanied by temporary normalization of cell kinetics of psoriatic keratinocytes[11]. UVB radiation has also been shown to alter the immune responses through a decrease in Langerhans cell number and function[12], alteration of the cytokine secretion pattern, and induction of apoptosis. UV radiation induces the production of interleukin 10 (IL–10), a cytokine that shifts the Th–1 environment back toward a Th–2 setting, and IL–15, which replaces the hyperactive T cell population with new unactivated T cells into the psoriatic plaques[10,11].

Narrowband UVB phototherapy for psoriasis is usually performed using cabins equipped with fluorescent lamps, 3 times a week starting with a dose equal to 70% of the minimal erythema dose (MED). MED represents the lowest dose of UVB able to produce a perceptible redness of the skin, and this can be determined for each patient by exposing small areas of the skin not previously sun exposed (buttocks, lower back, ventral foream) to a series of increasing doses of nbUVB. Using topical treatments in combination with phototherapy, clearance of the lesions is achieved in 12–16 weeks.

ReUVB REGIMEN

Several studies have confirmed that the combination of acitretin and nbUVB (ReUVB regimen) reduces the cumulative doses of both the drug and UV, allowing more rapid improvement of the psoriatic lesions[7]. The regimen is carried out treating the patient with acitretin alone (0.5 mg/kg bw) for 2 weeks, then the dose of acitretin is reduced to 0.3 mg/kg bw, and the nbUVB is added 3 times a week until complete resolution of the disease. As retinoids exert an anticarcinogenic effect, the ReUVB regimen could lower skin cancer risk resulting from longterm UVB therapy[13]. Moreover, the association of acitretin and nbUVB can be enhanced by topical treatments with calcipotriol, tacalcitol, and corticosteroids. Finally, it is important to take into account the importance of using retinoids, nbUVB phototherapy, or ReUVB as valid therapeutic approaches when other systemic treatments for psoriasis are contraindicated.

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