Editorial

G.

stüttgen

Berlin, FRG

From a clinical point of view, therapy with vitamin A acid originates from the thought that different pharmacokinetics of retinol in systemic or topical treatment would correspondingly entail a different metabolism and development of derivatives of vitamin A acid. Tumor development in the skin of mice caused by benzpyrene as well as therapy of ichthiosisform keratoses indicated that a therapeutic effect can only be achieved with systemic retinol administration. Henceforth, retinol metabolites applied topically resulted only in effects equivalent to those of systemic retinol treatment. Furthermore, clinical administration of tretinoin showed pharmacological characteristics exceeding the effect of retinol. The vitamin A story began in 1958/1959 with the discovery of its efficacy in retention hyperkeratoses and in senile (actinic) keratoses [1] and also its influences on normal skin with 'smoothing' effects on the skin surface. Topical tretinoin (0.05%) treatment of photoaged skin with atrophy, wrinkles and pigmentation by Kligman et al. [2] and the confirmation and consolidation by Ellis and Voorhees [3] inaugurated a new area in scientific dermatologic cosmetology. The clinical indications for treatment with tretinoin had to be compiled from an increasing number of anecdotic individual cases, in

which keratinization processes of malign as well as of benign nature showed therapeutic results. Furthermore, the stimulation of a lymphocytic infiltration of epithelial malignancies was soon related to immunologic parameters [4] (fig. 1-3).

In a daily dose of 100 mg orally, tretinoin suggested a therapeutic effect, which was generally more pronounced in retention keratoses. In the field of oncology, cancer en cuirasse and multiple basalomas showed a decrease in proliferation kinetics [4-6]. Individual adverse effects as severe edema on the 2nd day of administration (psoriasis) or unconsciousness lasting for 4 days with a completely stable circulatory system and subsequent awakening without complications necessitated careful observation exceeding the already present toxicological data. In retrospect, these side effects can be attributed to the toxicity of tretinoin, which is higher than that of the synthetic retinoids of today.

Local treatment was followed by skin irritations, which have their own problems in dermatologic practice; this situation was basically changed when Kligman et al. [7] introduced the local treatment of acne with isotretinoin in 1969. In 1978/1979, Peck et al. [8] initiated the oral treatment of cystic acne.

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Kissinger Strasse 12 S. Karger AG, Basel

D-14199 Berlin (FRG) 1011-0283/93/

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Fig. 1. Tumor induced by benz-pyren. The beginning of vitamin A acid research in Düsseldorf in 1958.

Fig. 2. First figure of improvement of congenital ichthyosiform erythroderma by topical vitamin A acid, verum against placebo (Düsseldorf, 1959).

Already in 1971, we recognized the superiority of isotretinoin (given orally: 10 mg) compared to tretinoin and informed La Roche of the pronounced scaling effect by topical application of isotretinoin (0.1-0.5%) on the horny layer. There, Bollag [9, 10] was the stimulator and constant advisor of our examinations limited to tretinoin, which was supplied by La Roche as well as BASF. The main efforts of La Roche concentrated on isotretinoin in Nutley, N.J., USA, while etreti-nate predominated in Europe. Bollag's [10] model of papillomas enabled the differentiation of retinoids always keeping oncological efficacy in mind [5]. The Symposium on Vitamin A Acid in Flims in 1975 revealed new perspectives [11]. The break in therapy of psoriasis developed shortly after this by way of oral etretinate [12]. The differentiation with respect to clinical aspects already indicated that the missing inhibition of sebum secretion by etretinate [13] could be attributed to a differentiation in receptors. The presentation of various receptors on protein and gene level [14-16] occurred concomitantly with the determination of the pharmacological spectrum. Vitamin A acid and its derivatives showed similarities to the nuclear receptors of thyrox-

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Fig. 3. Erysipelas carcinomatosa treated orally with 100 mg vitamin A acid daily and topically with 1% vitamin A acid ointment daily (Berlin, 1970). a Before treatment, b One month later, c Two months later. By histology, the improvement in the condition was documented only in the upper regions of the tumor. In the deeper layers (2 mm) an influence on the tumor cells with some nuclear pyknoeses and vacuolic degeneration.

ine and steroids, which belong to the super-family of nuclear hormonal receptors [17]. The synthetic retinoids proved that a change in the binding capacity is combined with changes in receptor selection and thus a differentiation in efficacy. The dose-dependent teratogenicity will remain a basic phenomenon, whereas the affinity of keratinocyte receptors, microvascular endothelial cells and the modulation of the immune system are changing phenomena which depend on the characteristics of each retinoid [18, 19].

In the skin, retinoids can be inactivated or converted to other active compounds, e.g. to isotretinoin after photoisomerization of topical tretinoin [20]. The problem of dose-dependent activities of the immune system was documented by inhibiting or activating effects of the same system on interleukin 2. The molecular mechanism in the treatment of the skin

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Table 1. A concept of the multifactorial action of retinoids

Synthetic retinoids	Tretinoin < Retinol	
	Variable receptor binding (CRBP, CRABP, RAR, RXR) <i>dependent</i> on target cells and type of retinoids with effects on:	
Cell differentiation and nroliferation (keratinocytes, skin neoplastic tissue)	Cell membranes (lvsosomes)	Immune system Morphogenetic (B lymnhocytes, action T lymnhocytes, cytokines, macrophages)

Φ	Φ	Φ Φ
Normalization of tissue homeostasis and	Membrane integrity	Immune modulation
Examples of indication:		
Hvnerkeratosis	Anticarcinogenesis	Antiphlogistic action
Acne	(reversible inhibition of promotion.	Autoimmune diseases (e.g. erythematodes)
Ichthvosiform keratosis	Cancer-preventing	
Psoriasis	Basalioma. xeroderma pigmentosum	
Photoaging		
Melasma		
Keratoakanthomas		

with topically applied retinoids can be explained by their influence on mesenchymo-epidermal interactions, activities on enzymes (e.g. transglutaminase) and finally by their influence on endothelial cells and angiogenesis of the microcirculation [2, 21]. The different effects of systemic or topical treatment encompass their own special problems. Topical application of tretinoin additionally to systemic therapy with retinoids can lower the systemic dose (table 1). Today, clinical aspects and assessment of biochemistry and molecular biology lay the foundation for the support and development of the ideal selective and specific therapy. This development is dependent on the creativity of 'abstract' scientists and experimental clinicians in order to meet the demands of the present society. This trend has also developed in the field of retinoids. It was a long way from the clinical observation, and 'simple' clinical aspects and the combined 'coincidental' therapeutical success to the recognition of the molecular structure of an hierarchical biological system to which the effect of retinoids can be counted today. The effect of retinoids as morphogenes underlines this situation which is integrated in the evolution of biological systems. Historical research on retinoids reveals that every retinoid has its own efficacy profile and spectrum of toxic effects. This information may, in the future, lead us to discover compounds with better therapeutic selectivity.

Today, importance of skin functions can be extended by the influence of retinoids on the skin associated lymphoid tissue or the skin immune system.

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The future role of retinoids does not only depend on monotherapy, retinoids can also participate as adjuvants to other therapeutical measures. The elementary mode of action of retinoids also changes the therapeutic threshold for other therapeutical principles. Skin and skin appendages are currently in the foreground of therapy. However, the therapeutic benefits in acute promyelocytic leukemia and in immune diseases, such as erythematodes for example, open the door to therapy in general. The following contributions based on several symposia and special chapters in books on advances in retinoids indicate examples for such aspects in the future [11, 18-27].

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