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SYSTEMIC RETINOIDS MECHANISMS OF ACTION THERAPEUTIC APPLICATIONS AND CLINICAL SIGNIFICANCE

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Retinoids, derivatives of vitamin A, play a fundamental role in modern medicine, particularly in dermatology and oncology. Acting at the cellular level, they regulate differentiation, proliferation, and apoptosis (Kang et al. 2021). Unlike topical formulations, systemic retinoids exert effects throughout the body after absorption into the bloodstream. Because of their profound biological activity, they are employed in the treatment of severe and refractory diseases such as nodulocystic acne, psoriasis, inherited keratinization disorders, and certain malignancies (Siegenthaler et al. 2019; Zouboulis 2020).

Systemic retinoids are traditionally classified into generations according to their chemical structure and receptor affinity. The first generation includes tretinoin, predominantly used in oncology, particularly in acute promyelocytic leukemia where it induces differentiation of malignant promyelocytes (Lo-Coco et al. 2013), and isotretinoin, the cornerstone of systemic therapy for severe acne and rosacea, which remains the most extensively studied and widely prescribed agent in this group (Layton 2009; Nast et al. 2020). The second generation consists of etretinate, historically used for severe dermatoses but withdrawn in most countries due to its high teratogenicity and extremely long half-life, and acitretin, its active metabolite, which is currently used in psoriasis, ichthyoses, and keratinization disorders (Orfanos et al. 1987; Mrowietz et al. 2014). The third generation is represented by bexarotene, a selective retinoid X receptor (RXR) agonist approved for cutaneous T-cell lymphoma, with receptor selectivity that confers anti-proliferative and pro-apoptotic effects in malignant cells (Duvic et al. 2001; Whittaker et al. 2016).

The pharmacological activity of systemic retinoids is mediated through nuclear receptors. Retinoic acid receptors (RARs), activated by all-trans retinoic acid and isotretinoin, regulate genes responsible for epithelial differentiation and keratinocyte maturation (Chambon 1996). Retinoid X receptors (RXRs), activated by ligands such as bexarotene, modulate transcription of genes involved in proliferation,

apoptosis, and immune responses (Altucci & Gronemeyer 2001). Through these pathways, retinoids influence gene networks controlling cell division, protein synthesis, sebaceous gland function, and inflammatory signaling. Clinically, their effects translate into normalization of keratinization, suppression of sebum production, and modulation of inflammatory cascades (Zouboulis & Bettoli 2015).

The therapeutic spectrum of systemic retinoids is broad. Isotretinoin is the treatment of choice for nodulocystic and conglobate acne resistant to conventional therapies, effectively reducing sebaceous gland activity, preventing follicular plugging, and providing long-lasting anti-inflammatory benefits (Layton 2009; Nast et al. 2020). Acitretin is widely used in plaque, erythrodermic, and pustular psoriasis, decreasing keratinocyte hyperproliferation and restoring epidermal differentiation, often in combination with phototherapy or other systemic agents (Mrowietz et al. 2014). Inherited keratinization disorders such as congenital ichthyoses and palmoplantar keratoderma also benefit from acitretin and related drugs, which reduce hyperkeratosis and improve skin flexibility (DiGiovanna 2001). In oncology, bexarotene is indicated for cutaneous T-cell lymphoma, inducing tumor cell apoptosis through RXR activation (Duvic et al. 2001), while tretinoin has revolutionized the treatment of acute promyelocytic leukemia by promoting differentiation of malignant blasts and achieving high remission rates when combined with arsenic trioxide or chemotherapy (Lo-Coco et al. 2013).

Despite their therapeutic efficacy, systemic retinoids are associated with a considerable risk of adverse effects. Teratogenicity remains the most critical limitation, necessitating strict pregnancy prevention programs and extended contraception after treatment discontinuation, for at least two months following isotretinoin and up to three years after acitretin (Choudhary et al. 2022). Mucocutaneous effects such as dryness of skin, lips, conjunctiva, and nasal mucosa are common and often dose-dependent (Layton 2009). Hepatotoxicity may occur, with elevation of liver enzymes and rare cases of hepatitis, making regular monitoring essential (Siegenthaler et al. 2019). Dyslipidemia, characterized by elevated triglycerides and cholesterol, is another frequent complication requiring routine lipid profiling (Zane et al. 2006). Neuropsychiatric effects, though rare, include depression, mood instability, and in exceptional cases suicidal ideation,

emphasizing the importance of psychiatric vigilance during therapy (Ng et al. 2016). Musculoskeletal complaints such as arthralgia, myalgia, and soft-tissue calcifications are seen with long-term administration (Bruno et al. 2014).

Contraindications to systemic retinoid therapy include pregnancy and breastfeeding, severe hepatic or renal impairment, uncontrolled hyperlipidemia, and severe psychiatric illness, particularly depression with suicidal risk (Nast et al. 2020). These restrictions highlight the need for careful patient selection, rigorous monitoring, and strict adherence to safety protocols.

Conclusion. Systemic retinoids therefore represent highly effective agents in dermatology and oncology, offering unique disease-modifying potential through their regulation of cellular differentiation, proliferation, and apoptosis. Their clinical utility, however, is counterbalanced by significant risks, particularly teratogenicity and metabolic toxicity, which necessitate vigilant supervision by clinicians. Future perspectives lie in the development of more selective retinoid receptor modulators with improved efficacy and safety profiles, potentially broadening therapeutic options while minimizing systemic harm.

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