Novel Drugs Targeting Retinoic Acid Receptors

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Retinoids, a group of small lipophilic molecules are essential for a variety of biological processes. Retinoids regulate gene transcription by binding to the nuclear receptors, the retinoic acid receptors (RARs) and retinoid X receptors (RXRs) (1). The RAR family consists of RAR \propto , RAR β , RAR γ , RXR \propto , RXR β and RXRy as well as their isoforms (1). The recent discovery and cloning of numerous receptor co-regulators, including co-activators and co-repressors has marked the begining of a new era in the studies of the action of retinoids. The efficacy of systemic retinoid therapy in a number of dermatological conditions is well established; however, potential side effects associated with their use limit their usefulness. There are three generations of synthetic retinoids.

First generation retinoids (2-4)

These are formed by the manipulation of the polar end group and the polyene side chain of vitamin A. Tetinoin, isotretinoin and alitretinoin are the first generation synthetic retinoids. Oral tretinoin was abandoned because of severe toxic side effects (hypervitaminosis-A syndrome). Isotretinoin has a terminal t1/2 in plasma of 10-20 hours and is completely cleared from the body within one month after the drug is stopped. Isotretinoin can cause adverse effects like cheilitis, dry skin, pruritis, dry nose, epistaxis, conjunctivitis, hair thinning, eye irritation, rectal bleed, hair loss, photosensitivity, pyogenic granuloma like eruptions at the site of minor trauma and acute lesion, periungal granulation, finger tip desquamation, nail brittleness, paronychia, contact lens intolerance, corneal opacities, papilledema, cataract, abnormal retinal functions, skeletal abnormality, pseudotumour cerebri, dyslipidemias, increased

liver enzyme, depressive symptoms and suicidal tendencies, teratogenic effects (hydrocephalus, microcephaly, atonia, small or absent external auditory canals, cardiac septal defect, aortic defects, facial dysmorphia, eye abnormality and bone abnormality), low IQ, parathyroid hormone deficiency and premature births. Alitretinoin is a natural pan-agonist for all 6 retinoic acid and RXR receptors. Its oral capsule has moderate activity against AIDS related kaposi sarcoma. It has antiproliferative, differentiating and apoptotic effects. However, it has substantial toxicity at doses >140mg/m²/day.

Second generation retinoids (2)

Etretinate and acitretin, also known as aromatic retinoids are synthesized by replacing the cyclic end group of vitamin A with various substituted and non-substituted ring systems. Etretinate remains stored in body deposits and has a terminal elimination t1/2 of about 100 days. It can be detected in serum in traces for as long as 3 years after cessation of therapy. Acitretin has terminal t1/2 of about 2 days. Etretinate and its metabolite acitretin are FDA approved for the treatment of psoriasis in adults. Etretinate (1.5mg/kg/day) and acitretin are also found to be safe in children. However, mucocutaneous side effects are reported with their use; but no laboratory abnormality is reported. In a clinical study etretinate (1 to 2 mg/kg/ day) was found to be effective in producing 90-100% improvement in lamellar ichthyosis, symmetric progressive erythrokeratoderma, darier's disease, pityriasis rubra pilaris and palmoplantar keratoderma. In a clinical trial on 12 patients with ichthyosis or palmoplantar hyperkeratosis, acitretin at 0.42 to 1.16 mg/kg/day proved to be effective. In 29 patients of disorders of keratinization, acitretin showed excellent response in low

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dose of < 0.4mg/kg/day. The most common side effects reported with its use are mucocutaneous dryness, minor liver and triglyceride laboratory abnormalities. Both etretinate and acitretin can cause diffuse thinning of hair; however, brittleness of nail is more with acitretin. Ocular side effects are also associated with the use of etretinate and acitretin; however, impaired colour perception is more with etretinate use. Both the drugs have potential to produce teratogenic effects. Because of rapid clearance acitretin has advantage over etretinate reducing delayed teratogenicity. However, small amounts of etretinate are found in patients after acitretin administration; thus avoid pregnancy for atleast 3 years after discontinuation of actretin therapy.

Third Generation Retinoids (5-7)

Tazarotene and adapalene are third generation retinoids approved by FDA as topical agents for psoriasis and acne respectively. Tazarotene is the first receptor sensitive retinoid for the topical treatment of psoriasis. On application it gets rapidly hydrolyzed to its main metabolite, tazarotenic acid which binds to RARs in the nucleus. Tazarotenic acid selectively binds to RARsß and r and exhibits little affinity for retinoid X receptors. RARy is the predominant type expressed in the human epidermis. By regulating gene transcription, tazarotene normalizes abnormal keratinocyte differentiation, reduces epidermal hyperproliferation and decreases inflammation, the three pathogenic factors in psoriasis, thereby producing a more normal expression of skin differentiation in psoriasis. Tazarotene gel 0.05% and 0.1% applied once daily for three months are found safe and effective in the treatment of plaque psoriasis in two multicenter, double-blind, randomized, vehicle controlled studies involving 660 patients. Tazarotene 0.1% was found to be more effective and slightly less tolerated than tazarotene 0.05% in two multicenter, double-blind, randomized, vehicle controlled studies. Adverse effects of skin irritation like pruritis, erythema and burning sensation are commonly reported with its use. Its average plasma concentration achieved after topical administration is 0.05ng/ml with plasma concentration of tazarotenic acid of 2.38ng/ml. More than 99% of tazarotenic acid is plasma protein bound.

Tazarotene and tazarotenic acid are metabolized to sulfoxides, sulfones and other polar metabolites and excreted in urine and faeces. Oral tazarotene is currently undergoing clinical testing for psoriasis in adults.

Bexarotene is a third generation agent approved for systemic treatment of Cutaneous T-cell lymphoma (CTCL) in adults. It is selective for the retinoid X receptors. Its mechanism of action in CTCL is believed to be multifold and may work by inducing differentiation and enhancing apoptosis of the malignant T cells, while inhibiting inflammation and decreasing abnormal proliferation of the surrounding keratinocytes. Its dose is 150mg/day orally. It has synergistic effect with PUVA (psoralen plus long wave UV-A) therapy in CTCL.

Such novel additions in the therapeutics may prove to be promising treatment strategies if used rationally.

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