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Retinoids-An overview of clinical applications in Dermatology

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Abstract:

Retinoids comprise a family of polyisoprenoid lipids that include vitamin A and its various natural and synthetic analogues. Although retinoids are having diversified clinical uses, they are important in dermatology as their main effect is on growth and normal differentiation of epithelial cells. Each retinoid has its own profile of pharmacological properties that determines its usefulness in clinical dermatology. Due to the existence of different types of retinoid receptors, response elements and cofactors, retinoid physiology is mediated by multiple discrete pathways and is highly complex. As a result, receptor selective retinoids are being developed which have more focused and targeted action and are likely to have a better therapeutic index. Oral retinoids such as isotretinoin and etretinate have promising results in the treatment of severe skin diseases like chronic acne, Darier's disease, rosacea and lupus erythematosus. Topical retinoids like tretinoin, tazarotene and adapalene are useful in number of skin diseases such as psoriasis, cutaneous lichen planus, melasma and many more. The development of receptor specific retinoids for topical treatment of psoriasis and/or acne may lead to interesting new compounds based on our current concepts of retinoid function. The major adverse effect of retinoids is teratogenicity; all other adverse effects are dose-dependent and controllable.

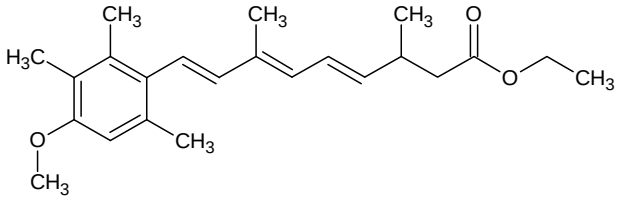
Keywords: *Retinoic acid receptor (RAR), Retinoid X receptor (RXR), Hyperkeratinization, pleiotropic effects, teratogenicity*

Introduction:

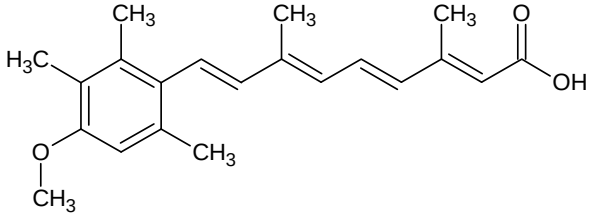
Retinoids include both naturally occurring molecules and synthetic compounds that have specific biologic activities that resemble to those of vitamin A. Vitamin A or retinol is a fat soluble vitamin. Its esterified form, vitamin A palmitate, is supplied in the diet by animal sources such as fish oil, eggs, butter, fortified magarine and animal liver. Vitamin A is also derived from carotenoid pigments, particularly β-carotene, which is found in many green and yellow vegetables.[2]

Vitamin A and its metabolites, retinal and retinoic acid are effective in various diseases but associated with severe toxic effects. A search for less toxic substitutes for vitamin A led to the development of the safer analogues.

Second Generation: These are mono-aromatic retinoids which include etretinate and acitretin. Through replacement of the β-ionone ring in all- *trans*- retinoic acid with an aromatic structure, newer retinoids with better therapeutic margins were synthesized in the 1970s.



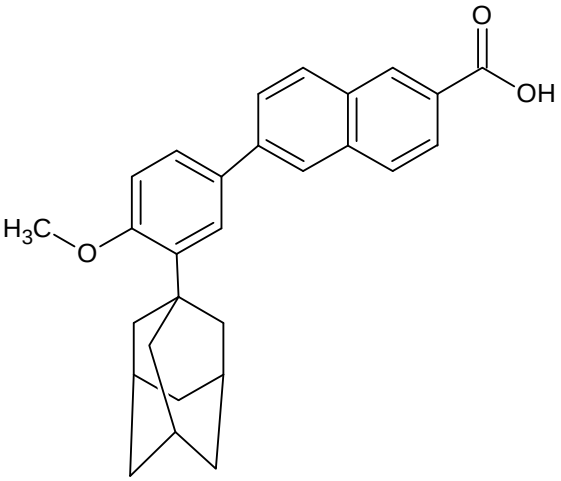
Etretinate



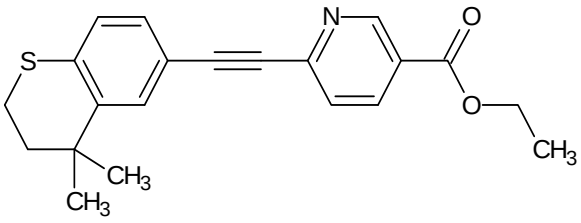
Acitretin

Etretinate and its free acid metabolite, acitretin, showed a therapeutic index ten times more favourable than that of all-*trans*- RA. Etretinate and acitretin became a standard treatment for psoriasis. Acitretin activates all three RAR subtypes but binds poorly to them[10] and has a great pharmacokinetic advantage because it is eliminated more rapidly than etretinate. The major metabolite of acitretin is 13-*cis*-isomer which is inactive.

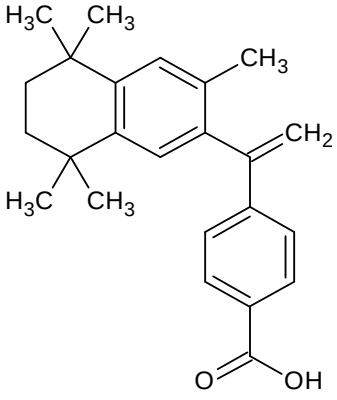
Third Generation: These are poly-aromatic retinoids called as arotinoids which include adapalene, bexarotene, tazarotene, temarotene, mofarotene.



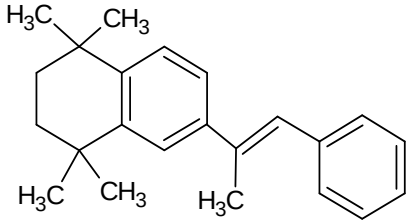
Adapalene



Tazarotene



Bexarotene



Temarotene

The discovery of retinoic acid receptors in 1980s allowed research directed towards receptor specific, third generation retinoids with a safer therapeutic index and a more selective action. In 1990s, researchers began devising molecules that would have greater conformational rigidity. As a result adapalene, a derivative of naphthoic acid having comedolytic, antiproliferative and anti-inflammatory properties[11] was found. It has similar efficacy to tretinoin but unlike tretinoin, stable in sunlight and tends to be less irritating. Bexarotene belongs to a subclass of arotinoids called rexinoids, because they bind to the retinoid X receptors which are responsible for controlling cell devision. It is the drug of choice in CTCL (cutaneous T-cell lymphoma).

Tazarotene is a novel, acetylenic retinoid, and is the first topical retinoid developed for the treatment of psoriasis. It targets keratinocyte and modulates the major causes of psoriasis. It is rapidly metabolized to an active free acid form tazarotenic acid, which is rapidly eliminated in animal species. Tazarotene selectively transactivates RAR β and RAR γ subtypes which are predominant receptors in epidermis and is inactive at retinoid X receptors (RXRs). It has low systemic absorption after topical administration. Topical doses are neither teratogenic nor carcinogenic and are not sensitizing or photosensitizing. The RAR nuclear receptor is the predominant receptor in the epidermis for which tazarotenic acid has high affinity. Temarotene and mofarotene are newer arotinoids awaiting

for FDA approval. Temarotene shows no sign of hypervitaminosis A and is not teratogeneic presumably due to lack of a polar group. This can be used clinically in the treatment of proliferative dermatological diseases. Mofarotene can be used as antineoplastic agent in lymphomas and breast cancer.

Therapeutic Effects:

Acne vulgaris:

Acne vulgaris is a common skin condition caused by changes in pilosebaceous units, skin structures consisting of a hair follicle and its associated sebaceous gland *via* androgen stimulation. It is characterized by non-inflammatory follicular papules, pustules and nodules in its more severe form. Severe acne is inflammatory, but acne can also manifest in non-inflammatory forms.[20]

Topical retinoids such as adapalene and tazarotene can normalize the follicle cell life cycle. Tazarotene showed greater efficacy and comparable tolerability and was cost effective alternative to tretinoin.[24] Although tretinoin and adapalene have similar efficacy in the resolution of acne, tretinoin result in a faster action in reducing comedones whereas adapalene is more chemically stable less photoliable, more lipophilic and also having greatest tolerability.[25]

Psoriasis:

Psoriasis vulgaris is characterized by erythmatous plaque with a severely scale. In severe cases the erythmatous eruption covers almost the entire body. In addition there are various pustular forms of psoriasis which may either localized or acute and generalized with high fever or systemic toxic effects. All forms of psoriasis respond well to either etretinate or acitretin. Acitretin is the retinoid of choice and is effective in severe psoriasis particularly pustular and erythrodermic types. Other forms require combination therapy with PUVA (psoralens + UVA) phototherapy [26-28] Tazarotene is available as topical formulation and can be used for mild to moderate psoriasis. Severe cases need oral retinoid therapy.

Darier's disease:

It is an autosomal dominant condition characterized by a defect in tonofilament-desmosome complex that connects epithelial cells in the epidermis. It is associated with dark crusty patches on the skin, sometimes containing pus in seborrhoic areas. These can become generalized and complicated by a foul odour from secondary infection and etretinate is effective. Acitretin is more effective for hyperkeratotic lesion. Adapalene or tazarotene are acceptable alternative topical retinoids[29, 30] used in Darier's disease.

Cutaneous T-cell lymphomas (CTCL):

These are heterogenous group of lymphoproliferative disorders characterized by localization of malignant T-lymphocytes to the skin at presentation. Retinoic acid, selective retinoids (All- *trans*-RA, 13-*cis*-RA, isotretinoin, etretinate and acitretin) are used for the treatment of CTCL. Orally administered bexarotene, the first synthetic highly selective X receptor retinoid to be approved by the FDA for CTCL and is active against the early cutaneous manifestations of CTCL. Bexarotene treatment induces apoptosis of CTCL cells with down regulation of its receptor. Synergistic effects in the treatment of CTCL have been reported[33] by using the combination of acitretin or isotretinoin with oral vit D_3 (calcitriol).

Premalignant and malignant skin lesions:

Etretinate and acitretin are effective in treatment of premalignant skin lesions, including human papillomavirus induced tumours and acitinic keratoses. In basal cell nevus syndrome and in xeroderma pigmentosum, these drugs reduce dramatically the incidence of malignant degeneration of skin lesions. Acitretin also

prevents the development of premalignant and malignant skin lesions in renal transplant recipients.[34]

Lupus erythematosus:

Lupus erythematosus is a chronic autoimmune inflammatory disease that prevents a striking diversity of clinical patterns with variable evolution and prognosis. Skin involvement occurs in 70-85% of all patients with lupus erythmatosus.[36] Interactions between genetic, infective and hormonal factors trigger alterations of immunoregulation that mediate the pathogenesis of this disease.[37] Retinoids are considered second line systemic drugs in treatment of DLE (Discoid lupus erythmatosus). Etretinate and isotretinoin are especially useful in hypertrophic lupus erythmatosus.

Side Effects:

The side effects of systemic retinoids qualitatively resemble hypervitaminosis A syndrome. The most prominent features of chronic hypervitaminosis A are dry scaling skin, cheilitis and loss of hair followed by bone pain, anorexia, headache, deplopia due to increased intracranial pressure. Hepatosplenomegaly often occurs with perisinusoidal deposition of lipids and fibrosis seen in biopsy specimens. In contrast to vitamin A the relatively non-toxic retinoids have few serious systemic side effects.

Teratogenic effects:

Teratogenicity is the major adverse effect caused by almost all systemic retinoids. Retinoids are not mutagenic but they cause serious fetal malformations, including major abnormalities of CNS, cardiac and ear defects.[42]

Mucocutaneous effects:

These are dose related, tolerable and reversible. Retinoids impair barrier function and enhance evaporation and causes dryness of skin and mucous membranes, thirst and increased percutaneous absorption of other topically applied compounds. Paronychia (changes in hair texture and increased skin fragility) can also occur with retinoid therapy. A more troublesome but uncommon side effect is dose dependent, reversible diffuse thinning of the hair that first appears 3-8 weeks[43] after the start of therapy especially with etretinate. Cheilitis is the earliest and the more frequent sign followed by blepharoconjunctivitis, dry eyes, dry nose and dry mouth. Photosensitivity is observed especially with isotretinoin and probably reflects the reduction of thickness of stratum corneum. Bexarotene appears to induce fewer mucocutaneous and ocular side effects than other classes of retinoids. Localized or extensive exfoliative dermatitis is the most common side effect with bexarotene.

Hyperlipidemia:

Depending on the type and dosage of retinoids, triglyceride levels are elevated in 50-80% and cholesterol levels in 30-50% of treated patients. Disturbance of blood lipid levels is generally higher with isotretinoin and bexarotene than with acitretin. In cases of severe retinoid induced hypertriglyceridemia, eruptive xanthomas and acute pancreatitis may occur. Discontinuation of therapy is required if triglyceride concentration reaches 800mg/dL.[41] Retinoids probably cause hyperlipidemia by increasing the expression of apolipoprotein C_3 which prevents uptake of lipids from very low density lipoproteins into the cells.

Hepatotoxicity:

Transitory abnormal elevations in serum transaminase levels have been reported in approximately 20% of patients treated with etretinate or acitretin and occur much less frequently with isotretinoin and bexarotene. Transaminase elevations more than three times the upper normal range should lead to discontinuation of retinoid therapy.

Musculoskeletal effects:

Musculoskeletal side effects can be seen with high doses and after an extended period of continuous treatment. Arthralgias and myalgias occur in upto 16% of patients receiving isotretinoin for acne.[44] Muscle pain and cramps rarely occur in patients taking etretinate or acitretin, however these muscle effects are frequent with isotretinoin, particularly in individuals involved in vigorous physical activity. Increased muscle tone, axial muscle rigidity and myopathy were reported to be related to etretinate and acitretin therapy. A more serious side effect is the development of skeletal hyperostosis in which nerve tone form in areas of ligamentous attachment. This occurs in longterm high dose treatment with isotretinoin.

CNS and other neurological effects:

CNS side effects are rare. Although individual signs of increased intracranial pressure such as headache nausea and vomiting are observed occasionally, the complete syndrome with papilledema and impaired vision is exceptional. Concomitant use of isotretinoin along with tetracyclins produced an increase in intracranial hypertension which is the major risk factor for development of pseudotumour cerebri (papilledema). Anecdotal reports suggest a casual association between isotretinoin therapy and severe depression with suicide attempts.[45]

Renal adverse effects:

Renal toxicity has not been a characteristic consequence of retinoid administration. Isotretinoin has been administered safely to patients with end stage kidney disease who were undergoing haemodialysis. However case reports describing reversible renal function impairment during etretinate therapy advice monitoring of renal function, particularly in patients with a history of renal disorders.

Precautions to be taken while treatment with retinoids:

1. Oral retinoids, being toxic medications, should be used cautiously. Patients should be made aware of the side effects and the precautions to be taken before starting isotretinoin.
2. As the systemic retinoids can cause deformities of the fetus, physician should confirm that their patients are not pregnant before starting the medication. The first dose of the medication may be started immediately after the menstrual period.
3. Use double birth control measures before and during and for a full month after the retinoid therapy.
4. Retinoids increase blood lipid levels. Hence intake of alcohol, oily, fried foods, eggs and red meat should be reduced during the treatment period especially in patients with high blood pressure and diabetes.
5. Other vitamin A containing vitamin supplements should not be taken while on retinoid therapy.
6. Start retinoid treatment with lowest strength. Later, a higher strength may be used when the skin becomes tolerant.
7. Avoid excess sun exposure while on the retinoids, as these can sensitize the skin to sunlight.
8. Apply non-comedogenic moisturizer like Sebium cream if irritation occurs.
9. Wait twenty minutes after washing the face before applying the topical retinoid.

Conclusion:

Vitamin A has long been known in dermatology to benefit disorders of keratinization. The low therapeutic ratio and the resulting acute and chronic toxic effects of vitamin A limited its clinical use. Although many retinoids are associated with hypervitaminosis A syndrome, newer retinoids with receptor specificity overcome many of these toxic effects. Retinoids with

Table 1: Data on commercially available oral and topical Retinoids

	Tretinoin	**Isotretinoin**	**Etretinate**	**Acitretin**	**Tazarotene**	**Adapalene**	**Bexarotene**
Chemical Configuration Ring structure Side chain End group Molecular weight	β-ionone β-cis Acid 300	β -ionone All-trans Acid 300	β-ionone All-trans Ethyl ester 354	Mono aromatic All-trans Acid 326	Poly aromatic Not applicable Ester 351	Poly aromatic Not applicable Acid 412	Poly aromatic Not applicable Ester 348
Therapeutic oral dose range (mg/kg/day)	–	0.5-2	0.5-1	0.3-0.75	–	–	300
Trade names	Renova® Retin A®	Accutane® Accure® Isotrex®	Tegison®	Soriatane® Aceret®	Tazorac®	Differin®	Targretin®
Available dosage form and strength	0.01% gel 0.025%,0.05 %,0.1% cream 0.05% solution	Capsules 5 mg, 10mg, 30 mg, and 40 mg. 0.05%gel	Capsule 10 mg Capsule 20 mg	Capsule 25mg	Gel 0.1% Cream 0.1%	Gel 0.1% Solution 0.1% Cream 0.1%	Cream 0.1%, 0.05% Gel 0.1% Capsule 75 mg

greater specificity for target organs and fewer systemic side effects are being developed by.means of modification of basic structures. Current retinoid research targets the development of receptor-selective retinoids for improving their therapeutic profile. Newer arotinoids like temarotene are without polar group and almost devoid of hypervitaminosis A syndrome and teratogenic effect which is the major draw back of retinoid therapy. Topical retinoids are being rapidly developed at present and seems promising for the future; their clinical application includes acne, aging, photo damage, precanceroses, skin cancer and disorders of skin pigmentation. The exact molecular mechanism of retinoids in dermatology is still under wraps. Research should be done on establishment of exact mechanism of retinoids in dermatological disorders so that to develop retinoids with more specific action and with least side effects.

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