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Review Article

Guidelines on the use of acitretin in Pakistan

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Abstract Actretin is a second generation retinoid which is commonly used in psoriasis and many other disorders of keratinization. The present review focuses on its uses, side effects and monitoring in the local perspective.

Key words
Acitretn, guidelines, psoriasis.

Introduction

Acitretin is a synthetic retinoid which has been around for about 20 years now and has completely replaced etretinate owing to its shorter half-life.[1] Recent evidence suggests that some of the drug is reconverted to etretinate especially if combined with alcohol.[2] Through its action on steroid-thyroid hormone superfamily nuclear receptors, it interferes with epidermal cell proliferation, differentiation, and cornification, hence its use in epidermal hyperproliferative conditions. It has also been shown to exert some immunomodulatory effects on skin.[3,4]

The cost, monitoring, and patient education and awareness are some of the factors which would restrict the use of acitretin, in Pakistan, as last resort and by expert dermatologists only. Since we do not have a governing body to monitor the dispensing, use, and monitoring of acitretin, therefore, the responsibility on the treating physician is immense. There are several guidelines published since the use of acitretin started but most are complicated and include measures which are not practical for a developing country like Pakistan. We present simplified guidelines which have been extracted from the evidence based literature and can be practically used by dermatology consultants in Pakistan.

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Peer review process

The initial guideline draft was prepared by Dr. Amer Ejaz and Dr. Tariq Malik and presented to the PAD membership for peer review. Dr. Asher Ahmed Mashhood, Dr. Dilawar Abbas Rizvi, and Dr. Zafar Iqbal Sheikh reviewed and amended the final document before submitting for publication.

Indications for use of acitretin

Acitretin is used in a number of dermatoses (**Table 1**).

1. *Psoriasis*
   Best evidence for the efficacy of Acitretin is in pustular psoriasis and erythrodermic psoriasis. However, long-term high dose therapy is required for optimal and lasting results. An optimal

Table 1 Acitretin use in cutaneous disorders supported by studies categorized by level of evidence.

Indications	*Comments and recommendations*	*Level of evidence*
Psoriasis	Current best evidence suggests use of acitretin in pustular and erythrodermic psoriasis. Advantage in combination with PUVA/NB-UVB/Calcipotriol. No advantage in combination with cyclosporine or methotrexate.[5]	1b
Palmoplantar pustulosis	Significant efficacy of acitretin shown against placebo in isolated RCTs.[5]	2b
Hyperkeratotic hand eczema	51% improvement in hyperkeratotic hand eczema compared to placebo has been shown in a single RCT.[8]	2b
Lichen planus	In severe and refractory lichen planus, significant efficacy shown against placebo in open studies.	3b
Darier disease	Lower doses (10-25mg) have shown marked improvement in small open studies.	3b
Lupus erythematosus	An RCT has shown better results with hydroxychloroquin but open study shows good results with Acitretin.	2b-
Pityriasis rubra pilaris	A single open study has shown marked improvement.	3b
Lichen sclerosus	Improvement has been shown against placebo in a controversial RCT.	2b-
Congenital ichthyoses	Open studies and anecdotal reports have shown improvement in several types of ichthyoses.	3b
Keratodermas	Open studies and anecdotal reports have shown improvement in several types of keratodermas.	3b

Level of evidence as specified by Center for Evidence Based Medicine.[17] 1b=individual RCT, 2b=individual cohort study including low quality RCT, 2b-=2b with inconclusive answer, 3b=individual case control study.

dosage is 50-75 mg daily for a period of 1 year.[5,6] At this dosage the incidence of adverse effects will be high and monitoring will have to be regular. In our scenario, male patients fulfilling the criteria could be put on the treatment but married women of child bearing age should be carefully evaluated in terms of patient commitment, spouse consent, both partners' education and awareness level, and possibility of regular timely follow-up visits with the prescribing consultant. In case of any doubt regarding any of these parameters, the patient should be offered alternate treatment.

2. *Other conditions*

Successful acitretin use has been reported in congenital ichthyosis, keratodermas, lichen planus, pityriasis rubra pilaris, Darier's disease, lichen sclerosus, and hyperkeratotic hand eczema.[7-11] In all of other uses of Acitretin apart from different forms of psoriasis, the evidence is either weak or sparse. We would recommend its use as a last resort in male patients while abstaining from its use in female patients as far as possible.

Contraindications

Pregnancy and lactation are considered absolute contraindications for the use of acitretin.[5] In our scenario, a married woman of child bearing age should also be considered a relative contraindication to its use. Its use should also be relatively contraindicated in children as several

reports suggest bone and skeletal changes with long term use.[12]

Adverse effects

1. *Teratogenicity* is the most important adverse effect. It is not dose related and due to reconversion of acitretin into etretinate, strict contraception up to 3 years must be observed. Retinoid embryopathy ranges from craniofacial dysmorphias, appendagial abnormalities to meningoencephaloceles. Risk is greatest in the first trimester. Two methods of contraception are mandatory, one of which should be primary (tubal ligation, vasectomy, intrauterine device, or hormonal therapy).[5]
2. *Transient and reversible elevation of liver enzymes* may occur in up to 15% of individuals. Rarely, treatment may have to be stopped or dose reduced.[13]
3. *Dryness of skin and mucous membranes* is commonly observed but rarely result in treatment discontinuation.[13]
4. *Skeletal adverse effects* range from arthralgia and myalgia to diffuse tendon calcification and hyperostosis. However, evidence suggests these changes can occur only after 2-4 years of therapy. For the same reason, use of Acitretin is restricted in children and should be undertaken only as a last resort and with full monitoring.[5,13,14]

Dosage and administration

1. Acitretin therapy should only be undertaken under the direct supervision of a qualified dermatologist. Informed consent should be taken and kept in record.
2. Effective adult dose in psoriasis is 25-50 mg daily. Treatment should be started at 25 mg daily and slowly increased every 2-4 weeks. It will take about 3-6 months to achieve the peak response.[15]
3. In Darier's disease and ichthyosiform disorders, a starting dose of 10 mg is more appropriate.[10]
4. If given in children under 12 years of age, starting dose of 0.5 mg/kg daily is appropriate which can be increased up to 1.0 mg/kg daily.[12]

Monitoring

This should be done under the direct supervision of a qualified dermatologist. In case of married females of child bearing age, urine pregnancy test one month before start of therapy and then every month till the duration of therapy is mandatory. All monitoring parameters need to be checked monthly for the first 3 months and then once every 3 months for the rest of the duration of therapy. Complete blood count, fasting lipid profile and liver enzymes (serum ALT) should be checked. Blood glucose needs to be checked only in diabetics and radiological assessment is not required to be undertaken.[15,16]

References

1. Kragballe K, Jansen CT, Geiger JM *et al*. A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre

study. *Acta Derm Venereol*. 1989;**69**:35-40.
2. Larsen FG, Jakobsen P, Knudsen J *et al*. Conversion of acitretin to etretinate in psoriatic patients is influenced by ethanol. *J Invest Dermatol*. 1993;**100**:623-7.
3. Chandraratna RA. Rational design of receptor-selective retinoids. *J Am Acad Dermatol*. 2010;**39**(4 Pt 2):S124–8.
4. Hardin J, Mydlarski PR. Systemic retinoids: chemoprevention of skin cancer in transplant recipients. *Skin Therapy Lett*. 2010;**15**:1-4.
5. Ormerod AD, Campalani E, Goodfield MJ. British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. *Br J Dermatol*. 2010;**162**:952-63.
6. Geiger JM. Efficacy of acitretin in severe psoriasis. *Skin Therapy Lett.* 2003;**8**(4):1-3.
7. Laurberg G, Geiger JM, Hjorth N *et al*. Treatment of lichen planus with acitretin. A double-blind, placebo-controlled study in 65 patients. *J Am Acad Dermatol*. 1991;**24**:434–7.
8. Thestrup-Pedersen K, Andersen KE, Menne T *et al*. Treatment of hyperkeratotic dermatitis of the palms (eczema keratoticum) with oral acitretin. A single-blind placebo-controlled study. *Acta Derm Venereol*. 2001;**81**:353-5.
9. Chapalain V, Beylot-Barry M, Doutre MS *et al*. Treatment of pityriasis rubra pilaris: a retrospective study of 14 patients. *J Dermatolog Treat*. 1999;**10**:113-7.
10. van Dooren-Greebe RJ, van de Kerkhof PC, Happle R. Acitretin monotherapy in Darier's disease. *Br J Dermatol.* 1989;**121**:375-9.
11. Bousema MT, Romppanen U, Geiger JM *et al*. Acitretin in the treatment of severe lichen sclerosus et atrophicus of the vulva: a double-blind, placebo-controlled study. *J Am Acad Dermatol*. 1994;**30**(2 Pt 1):225–31.
12. Lacour M, Mehta-Nikhar B, Atherton DJ *et al*. An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br J Dermatol.* 1996;**134**:1023-9.
13. Gupta AK, Goldfarb MT, Ellis CN *et al*. Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol.* 1989;**20**:1088-93.
14. Kullavanijaya P, Kulthanan K. Clinical efficacy and side effects of acitretin on the disorders of keratinization: a one-year study. *J Dermatol*. 1993;**20**:501-6.
15. Ling MR. Acitretin: optimal dosing strategies. *J Am Acad Dermatol*. 1999;**41**(3 Pt 2):S13-7.
16. Geiger JM, Czarnetzki BM. Acitretin (Ro 10–1670, etretin): overall evaluation of clinical studies. *Dermatologica.* 1988;**176**:182-90.
17. Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009). http://www.cebm.net/?o=1116).