REVIEW ARTICLE

Acitretin in Pediatric Psoriasis

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ABSTRACT

Pediatric psoriasis is a diagnostic and therapeutic challenge for dermatologists. One third of the total cases of psoriasis present before the age of sixteen. Approved medications list for severe cases of pediatric psoriasis is too short, with only few alternatives. Acitretin is a second generation synthetic retinoid that replaced its precursor etretinate more than two decades ago. It has proven and acceptable efficacy with quite reasonable safety profile. Acitretin is not yet approved by FDA for any indication in juvenile patients. However, it is still used as an off-label drug to control some intractable keratinization disorders. Recent guidelines and consensuses recommend the use of acitretin in pediatric psoriasis if benefit overweighs its potential risk. Indications in pediatric psoriasis, different dose schedules, duration of therapy and side effects are briefly discussed. In the era of novel therapies such as biologic and small molecules; acitretin still has its role in optimizing therapeutic outcomes for the treatment of pediatric psoriasis.

KEY WORDS: Acitretin, pediatric, psoriasis

INTRODUCTION

Psoriasis represents one of the most common and significant chronic inflammatory skin disorders; it affects 2% of the general population. One third of the cases of psoriasis presents before the age of 16 years which constitutes 4% of all dermatoses seen in children. Psoriasis in childhood is a disease of many forms, which may change and develop over time. Early diagnosis and management in children are particularly important to decrease long-term disease-related psychosocial problems and co-morbidities. İt may be difficult to diagnose on the first visit, since the frequencies of some morphological subtypes of psoriasis differ between adults and pediatric age group.[1-3]

The mean age of onset in pediatric psoriasis ranges from five to twelve years according to different studies; it affects both males to females in nearly equal ratio. A positive family history is variable across studies, varying from less than 10% in Northern İndia to as high as 51.4% in a recent multicenter study in United States. The initial areas of involvement are the scalp and the extensors of the legs. Classical plaque psoriasis is the most frequent clinical presentation followed by guttate psoriasis.[4-6]

Nail involvement is observed in 20-40% of the cases and 2.3% as the sole presentation. All types of nail changes are reported in pediatric psoriasis patients. The incidence of nail changes in male child is almost double that of female; while females get slightly more scalp lesions than males.[7] This may be explained by the differences in gender activities related to trauma or Koebnerization. Mercy *et al* encountered a rheumatologist-confirmed diagnosis of psoriatic arthritis in 10.5% of their

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group of patients.[8] However, psoriatic arthritis is reported in only 1-1.6 % pediatric psoriasis patients in other studies.[9]

Rare forms of the disease as erythrodermic psoriasis, flexural or inverse psoriasis, generalized and localized pustular psoriasis are reported in less than 1% of pediatric psoriasis. Pruritus is the most frequent symptom, and may be present in as high as 60-80% cases, especially among young children compared to adolescents.[7] Triggering factors especially streptococcal infection and stress were evident in pediatric psoriasis compared to adult onset psoriasis. The overall rate of co-morbidity in subjects with psoriasis aged less than 20 years is twice as high as in subjects of the same age without psoriasis. Pediatric psoriasis is associated with higher incidence of hyperlipidemia, hypertension, diabetes mellitus, obesity, and rheumatoid arthritis and Crohn disease.[10,11]

Acitretin is a second generation synthetic and mono-aromatic retinoid. İt is the active metabolite of etretinate, but 50 times less lipophilic. İt also has a shorter elimination half-life compared to etretinate. Etretinate was approved for the treatment of psoriasis in 1986, and replaced by acitretin in 1998; both have a considerable impact on the systemic treatment of psoriasis and other keratinization disorders because of its anti-proliferative action and effect on epithelial cell differentiation.[12-14]

Unlike other systemic anti-psoriatic therapies, acitretin is not considered to be cytotoxic or immunosuppressive. Acitretin has a different mechanism of action which is distinctive from other systemic drugs. And this may explain the reason behind its unremitting usefulness in the treatment of psoriasis in the era of biologics and signal blocking molecules.[15,16]

On the other hand, acitretin still lacks evidence based studies for its use in pediatric psoriasis. Only few studies have been done, and mostly on its precursor etretinate. However, long term usage in juvenile patients with keratinization disorders has guided dermatologist to adjust dosage and monitor side effects during off-label administration in pediatric psoriasis. Acitretin has been successfully used as monotherapy or combined with phototherapy or other systemic and topical anti-psoriatic agents.[12,14]

Studies on the pharmacokinetics of acitretin done in adult subjects reveal that its absorption after oral administration occurs in a linear trend up to 50 mg/d, and nonlinear at higher doses. It reaches peak plasma levels in 1-4 hours. More than 99% of absorbed drug is bound to plasma proteins. The rate of absorption is augmented 2-5 folds if acitretin is taken with food especially fatty food. Acitretin enters the cell by binding to cytoplasmic proteins, then binds to and activates nuclear receptors belonging to the superfamily of the transcription factors that include steroid, vitamin D3, and thyroid hormone receptors. Acitretin is metabolized primarily by the liver, giving rise to two metabolites: 13-cis-acitretin and etretinate. Both acitretin and 13-cis-acitretin are inter-convertible and widely distributed in adipose tissues, liver, kidneys and brain.[14,17]

Metabolism of retinoids is regulated by twenty genes; six of them encode the nuclear receptors; while other genes encode the drug catabolic pathways. The conjugates produced by the metabolism of acitretin and its metabolite 13-cis-acitretin are eliminated by the kidney (16% to 53%) or excreted into bile and ultimately eliminated in faeces (34% to 54%). Acitretin is eliminated after 49 hours (range, 33 to 96 hours), its metabolite,

13-cis-acitretin within 63 hours (range, 28 to 157 hours), and etretinate after 120 days (maximum up to 168 days). Trace amounts of acitretin are excreted in human milk (30-40 ng/mL), and it is estimated that the infant would ingest only 1.5% of the maternal dose. Traces of the drug have been found in seminal fluid at low concentrations (12.5 ng/mL).[16, 18, 19]

Etretinate is naturally produced in human from acitretin through a re-esterification process that varies in each individual. Etretinate has been detected in the plasma of patients on monotherapy with acitretin. The exact amount of alcohol that causes this reverse metabolism is yet unknown. The amount of etretinate produced is very small. Retinoid activity can persist for a long time even after the patient has stopped taking acitretin. İt was hoped that this shorter half-life would reduce the duration of the drug's teratogenicity; however, this goal has not been achieved.[15]

Mechanism of action is still hypothetical. İt is assumed that acitretin exerts its anti-psoriatic effect by anti-proliferative and immuno-modulatory actions. Anti-proliferative action reduces desquamation and the overall thickness of the lesion. İt also alters cellular metabolism, epidermal differentiation, and induces apoptosis. Moreover, it modifies T-helper cell responses, and suppresses polymorpho-nuclear leukocytes chemotaxis. İn addition, acitretin may also exert an indirect effect through genes that regulate angiogenesis and pro-inflammatory cytokines.[12-16]

Due to lack of evidence-based, high-quality studies, acitretin does not have Food and Drug Administration approval for any indication in children and is relatively contraindicated in females of childbearing age. Moreover, in the presence of data of skeletal side effects attributed to long-term etretinate treatment in childhood; the use of acitretin in pediatric psoriasis is not recommended by two recently published guidelines from Spain[16] and UK.[20] Nevertheless, the summary of product characteristics (SPC) for acitretin or Neotigason advises against the use of acitretin in children unless in the opinion of the physician, and the benefits significantly outweigh the risks.[21] However, taking into account the mounting data available after two decades of its use mainly in keratinization disorders in children, still many dermatologists believe that acitretin can be prescribed in a case to case basis as long as it is highly indicated.

Pediatric psoriasis patients are not a homogenous group in many aspects; the management involves education of both the children and their parents about the nature of the disease, and the effects and drawbacks of treatment. Also predisposing factors should be addressed such as stress, infection, trauma, and other environmental triggers.[7,9] Acitretin is considered as a treatment option for difficult-to-treat psoriasis, pustular forms of psoriasis and in unusual situations during the lifetime management of psoriasis. Acitretin therapy has also many limitations for its slow response and high side effects profile.[12,14]

Acitretin has been used in infants as old as six months and has shown preliminary efficacy in as short as three weeks.[22] As a monotherapy, acitretin has been used in pediatric psoriasis for initiation therapy in generalized pustular psoriasis, erythrodermic psoriasis, palmoplantar pustulosis, and guttate psoriasis. Acitretin monotherapy is also used as maintenance therapy for the same indications as well as in psoriasis vulgaris. As a combination with other therapeutic modalities; acitretin has been used to optimize efficacy in

wider range psoriasis phenotypes.[23-25]

When acitretin is added to topical calcipotriol, both show enhanced response; two thirds of the patients showed remission compared to 41% with acitretin monotherapy.[26] In a randomized double-blind placebo controlled trial of psoriasis patients receiving combination of acitretin and pioglitazone and placebo with acitretin in another arm of the study. After 12 weeks of therapy, reduction in severity index was 64.2% in the acitretin plus pioglitazone group compared to 51.7% receiving acitretin alone.[27]

Acitretin is a highly interesting candidate for combination therapy with biologics as it is not an immunosuppressive agent. Moreover, it has a chemopreventive property against skin carcinogenesis. Acitretin combined with etanercept has also been tried to decrease the frequency, cost and possible side effects of etanercept. A 24 week study in 60 patients showed that a combined therapeutic regimen with etanercept 25 mg once weekly and acitretin 0.4 mg per kg daily is as effective as etanercept 25 mg twice weekly, and more effective than acitretin alone.[28]

In a systematic review of systemic therapies for pediatric generalized pustular psoriasis, acitretin proved to exert high efficacy in controlling the disease in less than three months. İt is considered as one of the first line therapies by other authors for this indication.[29] Acitretin is used in this indication as monotherapy or in combination with prednisone and cyclosporine. With cyclosporine, acitretin was added after induction of remission as a part of sequential therapy to decrease the toxicity of cyclosporine.[30]

The National Clinical Guideline Centre (NCGC) discussed psoriasis assessment and management clinical guideline methods, evidence and recommendations in 2012, and stated that acitretin is only recommended for children (under 12 years) and young people (from 12-18 years) if methotrexate and cyclosporine are not appropriate or have failed; and for those patients with pustular psoriasis.[20] While the European expert group consensus recommends the use of acitretin in pediatric psoriasis only for children older than 10 years of age.[23]

A German expert group consensus confined their recommendation for the use of retinoids in children to pustular and severely hyperkeratotic types of psoriasis and in combination with PUVA[24]

The use of acitretin with different sources of ultraviolet has proved to be a useful combination with reasonable evidence.[23] In practice acitretin proved to exert synergistic effect when combined with both narrow band and broad band ultraviolet rays. Acitretin and narrow band UVB (Re-NB-UVB) was comparably effective to acitretin and PUVA (Re-PUVA) but with more safety profile and wider age range.[14,31]

Acitretin is used in different dose schedules for its use as monotherapy, combined therapy, sequential and maintenance therapy. Dose escalation strategy is based on the fact of individual variability in response and tolerance to the drug; though it is time consuming and may be not suitable for acute and severe cases. For initiation of monotherapy in GPP a dose of 0.5-1.1mg/kg is considered. A starting and constant dose of 0.5mg/kg and a dose of 0.3 mg/kg for maintenance therapy has also been recommended by European expert group consensus (2010). When acitretin is combined with other medications a dose of 0.5mg/kg or lower doses may be used.[12,13,23,32,33]

The duration of therapy depends on the indication, and it may range from 1-4 months in GPP, six

months for erythrodermic and guttate psoriasis and up to one year in palmo-plantar pustulosis. Longer durations or continuous therapy are infrequently prescribed in psoriasis. Treatment response should be assessed and monitored closely; if response is inadequate after 4 months at the optimum dose, acitretin should be discontinued.[13,15,16,32]

Initial monitoring of the drug prior to start medication, includes liver function tests, lipid profile, and glucose tolerance test. Pregnancy test is required for all females of childbearing potential taking into consideration social and psychological issues in more conservative countries. Follow up is done every 4 weeks for the first three months and the every 8 weeks thereafter. Glycosylated hemoglobin is repeated for diabetics, and patients with abnormal glucose tolerance. Initial and routine follow up X-ray for skeletal abnormalities and premature closure of the long bone is not necessary, controversial and may be harmful if done repetitively for patients. Only targeted X-rays for atypical musculo-skeletal aches is a helpful and safe approach. Growth monitoring is also advised for cases that need high doses and long duration of therapy.[15,16]

Mucocutaneous adverse effects of acitretin are common, reversible, and dose-dependent. They occur shortly after start of therapy and are mostly manageable, though in some instances may require dose reduction or cessation of therapy. They include cheilitis, stomatitis, gingivitis, xerosis, skin fragility, dermatitis, brittle nails, periungual pyogenic granuloma, palmo-plantar desquamation, hair thinning, hair falling, dry nose and epistaxis. Ocular toxicity are often serious, including blepharitis, conjunctivitis, intolerance of contact lenses, corneal opacities, papilledema, photophobia, cataracts, and abnormal retinal function, are very rare in children and typically reversible.[34-36]

Transient and benign backache, myalgia and arthralgia associated with mild elevation in the CPK may infrequently occur in physically active patients. On higher doses and longer duration ligamentous and tendinous calcification has been reported. A DISH-like syndrome has also been attributed to the use of acitretin. Other skeletal abnormalities which may occur are premature epiphyseal closure, osteopnea and exostosis.[35,36] The incidence of these skeletal changes is not exactly known, but some experts believe that it occurs in less than 1% of the patients. Concerns about the use of acitretin in pediatric population is mainly based upon reports and the issue remains unsolved.[37]

Transient hyperlipidemia, particularly hypertriglyceridemia, may occur in up to one-quarter of patients, but is dose dependent and reversible with dose reduction or discontinuation. Hyperlipidemia is proportional to the dose of acitretin and usually reverses within 4-8 weeks after discontinuation. Hypercholesterolemia, has been reported in 10-30% of patients treated with acitretin.[34,35,38] Transient, usually reversible, elevation of liver enzymes may occur in up to 15% of patients receiving acitretin.[39]

Retinoid embryopathy can result in craniofacial dysmorphias, appendageal abnormalities, absence of terminal phalanges, malformations of the hip, meningo-encephalocele, and multiple synostoses.[40,41] The duration of teratogenic potential is unidentified; it is advisable to continue on contraception for at least three years following cessation of acitretin therapy.[42] Rare complications as pseudotumor cerebri has recently been reported in one child on long term therapy for keratinization disorder.[43]

CONCLUSION

Acitretin is non-immune suppressive anti-psoriatic drug. It is mainly indicated in pustular forms of the disease as well as other forms like erythrodermic psoriasis. It is used as monotherapy or combined with other topical, systemic or phototherapy, especially with combination with topical calipotriol and NB-UVB. Side effects are multiple and mostly reversible. Concerns about the use of acitretin in children lacks solid evidence and is controversial to date. Acitretin is still considered as a therapeutic option in treatment pediatric psoriasis in the era of modern therapies.

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