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Review

Acitretin in psoriasis: an evolving scenario

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Abstract

Acitretin, an active metabolite of etretinate, is the most widely used systemic retinoid in the treatment of psoriasis. There are several unique characteristics of this drug, which set it apart from other options in the therapeutic armamentarium of psoriasis. It is highly efficacious as monotherapy in some specific clinical subtypes of psoriasis. It has dose-sparing effects when used as combination therapy with conventional systemic drugs as well as the biologics. It is a good option for long-term maintenance therapy. Side effects are common but usually mild and can be managed by its proper dosing and monitoring. With appropriate patient selection, gradual dose escalation, and patient counseling, we can deliver good results in psoriasis with this useful drug. This review gives a comprehensive recount of acitretin use in the present era of biologics in psoriasis.

Introduction

Psoriasis is a common, chronic inflammatory disease of skin having worldwide prevalence of 1–3%.[1] It is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, infiltration of T lymphocytes, and various endothelial vascular changes in the dermal layer. Psoriasis is mediated by interplay of genetic, immunological, psychological, and environmental factors. Release of T lymphocytes and the cytokines and chemokines appears to be the principal driver of lesion development and persistence along with endothelial cells, neutrophils, natural killer T cells, and selectins such as intercellular adhesion molecule-1 play an adjunctive role. Accumulating evidence suggests interleukin-17A plays a key role in the pathogenesis of plaque psoriasis.[2]

A wide range of treatment modalities are available that can be either topical or systemic or a combination of both. The majority of therapeutic options in psoriasis are immunosuppressant and carry significant adverse effects and toxicity profile. However, retinoids in general and acitretin in particular offer the advantage of being a non-immunosuppressive drug with a better safety profile. Etretinate was the first oral synthetic retinoid used in the treatment of psoriasis and other disorders of keratinization in the 1970s. Acitretin is the free and active metabolite of etretinate, and it became the most widely used systemic retinoid in the management of psoriasis due to its better pharmacokinetic profile.[3] It is USFDA approved for the treatment of psoriasis, and its niche in the management of psoriasis has been reviewed by many authors.[4–6] Acitretin is probably the safest among the first three FDA-approved systemic drugs for psoriasis especially when considering its continuous use over many years. We present the role of acitretin in psoriasis management in the era of biologics and discuss its safe and efficacious use in varied psoriasis clinical types.

Pharmacology

Acitretin has a bioavailability of 20–90% after oral intake, bioavailability being enhanced by fat rich food.[7] It reaches peak plasma levels in 1–4 hours. More than 99% of absorbed drug is bound to plasma proteins.[8] Half-life of acitretin is 2–4 days, which is much shorter than that of etretinate (120 days). It is 50 times less lipophilic than etretinate, hence eliminated more rapidly. It is metabolized to 13-*cis*-acitretin, which is interconvertible with acitretin, and both are widely distributed in the body and then excreted in feces and urine. One month after cessation of therapy, the residual plasma concentration falls below detection limit, thereby lowering the risk of teratogenicity. However, *in vivo* re-esterification of acitretin to etretinate can take place, thus prolonging the stay of the

drug in the body. Alcohol is a contributing factor but not a necessary precondition for re-esterification.[9,10] The exact amount of alcohol that causes this reverse metabolism is not known.

The exact pathogenesis of psoriasis is not yet elucidated, though keratinocyte hyperproliferation is the result of a complex interplay of several factors. The mechanism of action of acitretin also remains unknown. It enters the cells by non-receptor-mediated endocytosis where it binds to cytosolic proteins, which carry it to nucleus, and there it activates nucleic acid receptors. Two classes of retinoid nuclear receptors have been identified: retinoic acid receptors and retinoid X receptors. Each of these classes is comprised of α, β, and γ types and various isoforms.[11] Retinoid receptors regulate transcription of genes bearing short DNA sequences in their promoter region known as retinoic acid response elements.

Psoriasis involves altered vitamin A metabolism resulting in high levels of retinoic acid in psoriatic plaques compared to normal skin.[12] Thus the fact that retinoid therapy is effective for psoriasis treatment appears to represent a paradox. Acitretin has multiple effects on epidermal cell growth and differentiation possibly responsible for its therapeutic action in psoriasis.[13,14] It induces and modulates expression of growth factors and their receptors. These include inhibition of cytokine-induced synthesis of retinoic acid, stimulation of metabolism, and buffering of cytokine-induced increase in retinoic acid by increasing CRABP 2 and altered metabolism of endogenous retinoids at the level of degradation. The overall effect of acitretin on psoriatic epidermis results in reduction of proliferation rate in acanthotic epidermis by downregulating the number of cycling cells, promotes terminal differentiation of keratinocytes, regulates desquamation of corneocyte, and decreases the thickness of stratum corneum and inflammation in epidermis and dermis. In addition, the immunomodulatory and antiangiogenic action of retinoids may contribute to their efficacy.[15] Acitretin is available in oral capsule formulation (10–25 mg).

Efficacy as monotherapy

Acitretin can be used in moderate to severe plaque-type psoriasis that cannot be managed by topical treatments or phototherapy, psoriatic erythroderma, generalized pustular psoriasis (GPP), palmoplantar (pustular) psoriasis, and nail psoriasis. Use of acitretin is contraindicated in certain conditions (Table 1); it should be used with caution in patients on concomitant medications that interfere with retinoids or on hepatotoxic drugs, patients with poorly controlled diabetes mellitus, and patients with alcohol abuse.[3,16] All patients receiving acitretin should have appropriate baseline and follow-up monitoring (Table 2).[16]

Table 1 Contraindications to acitretin therapy

Absolute	Pregnancy
	Lactation
	Hypersensitivity to the preparation or to other retinoids
Relative	Women of childbearing potential who cannot guarantee adequate contraception during and up to 3 years following discontinuation
	Impaired liver functions
	Impaired kidney functions
	Severe hyperlipidemia

Table 2 Laboratory monitoring of acitretin

Baseline monitoring	Follow-up monitoring
• History and physical examination	• History and monthly physical examination
• Pregnancy test (if indicated)	• Liver function tests, lipid profile at 2 weeks interval for first 8 weeks; then every 6–12 weeks
• Complete blood cell counts	• Complete blood cell counts, kidney function tests every 3 months
• Liver function tests	• Pregnancy test monthly
• Kidney function tests	
• Lipid profile	

Chronic plaque-type psoriasis

Initially when acitretin was introduced, four randomized controlled trials compared its efficacy with that of etretinate and found the two drugs to have similar efficacy.[17–20] Further studies have been conducted involving use of acitretin as a single agent in different dosages for the treatment of different clinical types of psoriasis (Table 3a,b).[21–28] Efficacy of acitretin depends on the clinical type of psoriasis. Erythrodermic and pustular psoriasis exhibit good response to acitretin, while the drug is only moderately efficacious in chronic plaque-type psoriasis.[21–28]

Response to acitretin as well as adverse effects have been shown to be dose dependent, with higher doses yielding greater improvement and more frequent clearance of psoriasis lesions along with a greater frequency of adverse effects.[21,24,25] Initially, the patient should be started on low dosage (10–25 mg/day) and gradual dose escalation (maximum 75 mg/day) done according to response of the disease and tolerance of the patient. Some patients may have initial worsening of the symptoms in the form of burning, increased erythema, and plaque expansion, but the improvement starts as soon as the drug is continued. In addition, it has been observed that patients on continued medication develop tolerance to side effects. So, proper dosing of acitretin is required to

Table 3 Efficacy studies of acitretin as monotherapy for psoriasis

Author	Number of patients	Dose regimen	Results
(a) Efficacy studies of acitretin as monotherapy in plaque-type psoriasis			
Gollnick *et al.*,[19] (double blind randomized multicentre study)	175	10, 25, or 50 mg/day of acitretin or 50 mg/day of etretinate × 8 weeks	No significant difference in response after 8 weeks of treatment, with PASI 50 achieved in 50% (10 mg/day group), 40.5% (25 mg/day group), and 53.8% (50 mg/day group). Patients treated with etretinate had PASI 50 in 61.1%.
Goldfarb *et al.*,[21] (double blind RCT)	38	Placebo, 10, 25, 50, or 75 mg/day × 8 weeks followed by open-label phase with 50 mg/day × 16 weeks.	Significant reduction in PASI score compared to placebo in 50 and 75 mg group. Increased frequency of side effects at higher doses (>50 mg/day).
Olsen *et al.*,[22] (double blind placebo RCT)	15	Acitretin (25 or 50 mg/day) or placebo × 8 weeks followed by open-label phase with acitretin 25–75 mg/day × 12 weeks	Reduction in scaling (33%), erythema (28%), and thickness of plaques (38%) with minimal change in% of BSA involved at end of 8 weeks. Reductions in scaling (42%), erythema (50%), and thickness of plaques (53%) with 44% reduction in BSA involved at end of 20 weeks.
Torok *et al.*,[23]	14	35–50 mg/day × 12 weeks	Remission in six patients
Berbis *et al.*,[24]	66	Three groups of patients Group 1, 10 mg/day for 2 weeks, then 30 mg/day for 2 weeks, followed by 50 mg/day for 2 weeks. Group 2, 30 mg/day for 6 weeks. Group 3, 50 mg/day for 2 weeks, then 30 mg/day for 2 weeks, followed by 10 mg/day for 2 weeks. During next 6 weeks dose adjusted to response (10/30/50 mg/day) in 3 groups.	Comparable efficacy in three groups. 81, 87, 88% improvement in mean PASI at 12 weeks in groups 1, 2, and 3 respectively. Patients in dose escalation group (group 1) experienced lowest toxicity.
Dogra *et al.*,[25]	61	Three groups of patients given acitretin for 12 weeks Group 1, 25 mg/day Group 2, 35 mg/day Group 3, 50 mg/day	PASI 75 in 47%, 69%, and 53% in groups 1, 2, and 3 respectively. Safety profile of 35 mg/day dose higher than 50 mg/day dose.
(b) Studies of acitretin in mixed clinical types of psoriasis			
Lassus *et al.*,[26] (double blind placebo RCT)	$n = 80$ Plaque type (70), Pustular (4), Erythrodermic (6)	Placebo, 10, 25, or 50 mg/day × 8 weeks to 20 patients each. Dose adjusted to response for next 4 months.	Efficacy of 25 and 50 mg group similar and significantly more than the placebo group. No significant difference between placebo and 10 mg group. Severe side effects more frequent in 50 mg/day group
Geiger *et al.*,[27] (review of 12 clinical trials)	539 psoriasis patients and 200 received acitretin. Plaque type (183), Pustular (11) Erythrodermic (6)	10–50 mg/day × 2–6 months	Complete remission in 31.5%.Marked improvement or remission in 100% of patients with pustular psoriasis, and 83.3% of erythrodermic psoriasis patients. 76.5% patients with other forms of psoriasis achieving marked improvement or remission.

Table 3 Continued

Author	Number of patients	Dose regimen	Results
Kragbelle *et al.*,[17] (double blind randomized comparison)	n = 168 (127 acitretin, 41 etretinate). Plaque type (150), Pustular psoriasis (15), Erythrodemic (3)	40 mg/day × 4 weeks, Adjusted to maximum improvement and continued for 8 weeks	76% and 71% reduction in PASI score in acitretin and etretinate group respectively
Murray *et al.*,[28] (open-label study)	n = 63 Plaque type (56), PPP (5), palmoplantar psoriasis (1), Erythrodemic (1)	50 mg/day × 4 weeks, then dose adjusted according to response (10–70 mg/day) and continued for 12 months	57% reduction in PASI at end of 12 weeks, 76% reduction at end of 12 months. Marked improvement in >70% patients. 22% withdrew due to side effects

PASI, psoriasis area and severity index; PPP, palmoplantar pustular psoriasis; RCT, randomized controlled trials.

establish a balance between the drug's efficacy and its toxicity in individual patients. Among patients with chronic plaque-type psoriasis the best response is seen in one having small and thin plaques, and stable disease. In addition, the response is slow, and it may take 3–6 months to achieve maximal disease control. The patient should be counseled regarding the efficacy, side effect profile, and treatment duration before starting the drug to have better compliance.

Erythrodermic psoriasis

Erythrodermic psoriasis is a severe form of psoriasis with high morbidity and mortality. There is lack of high-quality literature on its management probably because of its low incidence. Cyclosporine (CYC), infliximab, and methotrexate (MTX) are the fast acting agents for its treatment. Acitretin is also considered as a first-line drug in a selective group of patients, though it acts slowly.[29] There are no head-to-head comparisons available between these first-line drugs. In individual cases, choice is made depending upon the clinical picture, comorbidities, and financial constraints.

Those who have an acute and severe presentation should preferably be treated with CYC and infliximab. Those patients in whom there is absolute or relative contraindication for CYC and infliximab or who have subacute or chronic onset of erythroderma and do not have significant metabolic complications warranting early treatment can be safely managed with acitretin. Geiger *et al.* reported marked improvement or complete remission in 83.3% patients when treated with acitretin monotherapy.[27] Recently, acitretin is being used in combination with infliximab in patients with erythrodermic psoriasis with excellent response.[30]

Pustular psoriasis

Generalized pustular psoriasis

Acitretin is one of the treatments of choice in pustular psoriasis. There are case series of treatment of GPP with etretinate.[31,32] Wolska *et al.*[31] treated 18 patients of GPP with etretinate in an open label study. By the end of the 4-month follow-up period, 17 patients had disease remission. In an uncontrolled, retrospective case study of 385 patients with GPP, etretinate, MTX, CYC, and oral psoralen + ultraviolet A (PUVA) were effective in 84, 76, 71, and 46% of patients, respectively.[32] Many other authors have reported a good response of pustular psoriasis to acitretin.[17,27]

Unlike plaque-type psoriasis, in GPP acitretin should be given in high starting doses, as it requires aggressive treatment. As the disease is controlled, the dose is gradually tapered down to the lowest effective dose.

Palmoplantar pustular psoriasis

Etretinate was found to be effective in palmoplantar pustular psoriasis (PPP) in two randomized controlled trials.[33,34] It rapidly reduces the pustulation and hyperkeratosis. Acitretin is also a good choice in PPP. Lassus and Geiger[35] did a double blind randomized comparison between acitretin and etretinate in 60 patients with PPP. Patients received 30 mg/day of acitretin or etretinate for four weeks and then variable doses according to response for the next eight weeks. At the end of the 12-week study period, both the drugs led to an equally good response. PPP can sometimes be very refractory to treatment and if response to monotherapy is not satisfactory, then combination therapy (retinoid PUVA, re-PUVA) should be considered. Ettler and Richards used acitretin in combination with topical PUVA for the treatment of PPP with good response.[36]

Nail psoriasis

Nail involvement occurs in up to 78% of patients with psoriasis, is more common in patients with psoriatic arthritis, and may be the only sign of psoriasis in some patients.[37,38] It receives little attention compared to plaque psoriasis and is relatively more resistant to therapy, slow to respond, and therefore frustrating to treat. Retinoids have been reported to be effective in nail psoriasis in few studies.[37,38]

The response of cutaneous plaque psoriasis is dose dependent with greater response at higher doses. However, in the treatment of nail psoriasis, acitretin can sometimes produce worsening of nail psoriasis with paronychia and nail fragility when used at the dosages recommended for skin psoriasis. Tosti *et al.*[39] treated 36 patients with moderate to severe nail psoriasis with low dose (0.2–0.3 mg/kg per day) acitretin. Clinical evaluation at six months showed complete or almost complete clearing of the nail lesions in nine patients (25%), moderate improvement in nine (25%), mild improvement in 12 (33%), and no improvement in six (11%).

López *et al.*[40] reported a rapid response of severe nail psoriasis to 25 mg/day of acitretin in a patient who was resistant to topical therapy and systemic MTX; although it was a single patient report, the response was quick and dramatic. Therefore, acitretin in low doses given for long periods is a good choice in patients seeking treatment for nail psoriasis primarily.

Childhood psoriasis

According to British Association of Dermatologist guidelines,[41] acitretin is not recommended in children, as there have been occasional reports of bone changes, including premature epiphyseal closure, skeletal hyperostosis, and extraosseous calcification in children on long-term treatment with etretinate.[42–44] If the benefits significantly outweigh the risks, then acitretin may be given, and the child should be carefully monitored for any abnormalities of growth parameters and bone development, including plotting growth charts. There are few reports of acitretin being given for infantile pustular psoriasis for short periods with good results.[45,46]

Efficacy as combination therapy

In combination therapy, two or more agents with synergistic or complementary action are used concomitantly, allowing lower dose and toxicity sparing regimen of each of the agents.[47] Acitretin has been used in combination with topical therapies, systemic conventional drugs, photo (chemo)therapy and, recently, in combination with biologics to enhance the efficacy and limit the adverse effects.

Topical drugs

Acitretin can be combined with topical calcipotriol for better clearance of psoriatic plaques.[48] A randomized, bilateral paired comparison was conducted by Rim *et al.*,[49] involving 40 patients with psoriasis who received calcipotriol and acitretin combination therapy and 20 patients with psoriasis who received acitretin alone. After 52 weeks, 24 patients (60%) in the calcipotriol + acitretin group and eight (40%) in the acitretin monotherapy group achieved complete clearance. The duration of treatment and total dose of retinoid required to achieve clearance were lower in the calcipotriol plus acitretin combination group, though it was not statistically significant.

Conventional systemic drugs

Acitretin is used as a combination therapy in conjunction with several conventional systemic drugs as well as with the biologics for psoriasis (Table 4). It is a good option for combination therapy, as it does not add to the immunosuppression, while reducing the total dose requirement of antipsoriasis drugs. In addition, lower dosage of acitretin is required when used in combination, thereby increasing its tolerability and compliance to therapy.

Acitretin FDA-approved prescribing information does not recommend use of MTX in combination with acitretin in view of enhanced liver toxicity. Data on this combination therapy are scarce. Lowenthal *et al.*[50] reviewed the clinical data of 18 patients with psoriasis who received acitretin and MTX. In this series of patients, combination therapy was well tolerated and effective. There were no new or unusual adverse events noted, including significant hepatotoxicity. The combination may be used when either drug alone is not producing disease control, for short intervals, and with close monitoring for the side effects.

Table 4 Studies of acitretin as combination therapy other than with photo(chemo)therapy and biologics

Drug combination	Study	Dose regimen	Results
Acitretin + calcipotriol	Rim *et al.*,[49]	40 received combination and 20 received acitretin alone for 52 weeks	60% in combination group and 40% in monotherapy group achieved complete clearance
Acitretin + methotrexate	Lowenthal *et al.*,[50]	18 patients received acitretin 25 mg o.d./e.o.d. along with methotrexate 7.5–25 mg/weekly for average duration of 9 months	Combination well tolerated and effective. No new or unusual side effects.
Acitretin + hydroxyurea	Yamauchi *et al.*,[52]	Acitretin 25 mg and hydroxyurea 500 b.d.	Effective in plaque and pustular psoriasis, careful monitoring of blood counts required
Acitretin + pioglitazone	Mittal *et al.*,[54]	22 patients – acitretin (25 mg/day) with placebo and 19 patients – acitretin (25 mg/day) with pioglitazone (15 mg/day) × 12 weeks	64% reduction in psoriasis area and severity index score in combination group, 52% reduction in placebo + acitretin group

CYC and acitretin are commonly used as sequential therapy rather than as combination therapy. Besides reducing the dose of individual drug, the additional advantage of combination is that acitretin mitigates the carcinogenic risk with cyclosporine[51]; both drugs can potentially derange lipid profile, so combination is to be used for short periods with close laboratory monitoring.

Hydroxyurea is uncommonly used for psoriasis. It is used as a second-line drug in case conventional first-line therapy is not tolerated or fails and biologics cannot be given due to financial constraints. There is limited data on safety and efficacy of the combination of acitretin and hydroxyurea.[52] The combination therapy requires careful monitoring of complete blood counts.

Metabolic syndrome is common in patients with psoriasis.[53] In a randomized double-blind placebo-controlled clinical trial, a combination of acitretin with pioglitazone was a significantly more efficacious, convenient, and relatively safe option especially in patients with psoriasis with the metabolic syndrome.[54] Fewer numbers of patients in the combination group (37%) had an initial flare compared to acitretin plus placebo group (50%) Both the drugs have antiproliferative, prodifferentiating, anti-inflammatory, and antiangiogenic activity and thus may have additive efficacy in patients with psoriasis. Scaling was the first parameter to improve, followed by erythema and induration. Thinner plaques tended to respond earlier than thicker plaques. In addition, smaller lesions responded earlier than larger ones. Lesions over the extensor aspects of the elbows and knees were the last to respond. Characteristically, larger plaques cleared from the center outward.

Photo(chemo)therapy

Acitretin has been used in combination with PUVA, broadband UVB, and narrowband UVB (NB-UVB). The combination of retinoids with photo(chemo)therapy enhances the efficacy of phototherapy and thereby reduces the cumulative UV dose and duration of the therapy needed to treat chronic plaque psoriasis (Table 5).[55–62] In addition, the combination has got retinoid dose-sparing effect as usually 10–25 mg/day suffices compared to the 25–50 mg/day required when given as monotherapy. This diminishes the side effect profile, which is primarily dose related in the case of acitretin.

The combination of acitretin and PUVA (re-PUVA) is very effective in thick plaque psoriasis and is generally considered the treatment of choice for severe or extensive cases.[55–57] The patient is started on low-dose acitretin (10–25 mg/day) alone for 10–14 days, and then PUVA treatment is added and continued until clearance of psoriasis lesions. Re-PUVA leads to faster clearance with a greater number of (>90%) patients clearing at the end of 12 weeks, and the cumulative UV dose is reduced by about 50%.[55] In addition, acitretin has the advantage of decreasing the risk of carcinogenicity along with attenuation of photoaging associated with phototherapy.[63,64] Muchenberger *et al.*[65] used a combination of bath PUVA with acitretin to treat four patients with severe erythrodermic, pustular, or plaque-type psoriasis. They found the combination to be very effective with >90% improvement after four weeks, and no relapse was seen with up to three months of therapy.

The combination of acitretin with broadband UVB has been used effectively in treating severe forms of plaque-type psoriasis.[58,59,66] This regimen has the advantage in allowing use of phototherapy without the requirement of oral psoralen as well as lower risk of carcinogenesis as compared to PUVA. A combination of BB-UVB with acitretin works significantly better than the BB-UVB alone in terms of cumulative UV dose, percentage of patients going into complete remission, and total time to treatment.

The experience with combination therapy of acitretin with NB-UVB is limited. Retrospective data analysis of 29 patients with plaque-type psoriasis who were treated with NB-UVB alone or in combination with acitretin, revealed

Table 5 Studies of combination of acitretin with photo(chemo)therapy

Study design	No. of patients	Study duration (in weeks)	Treatment duration (in days)	Mean no. of treatments	Cumulative UV dose (J/cm^2)	No. of patients cleared at end-point
Combination with PUVA						
Saurat *et al.*,[55]						
Acitretin + PUVA	20	12 weeks	47.8 ± 2.3	13.7 ± 0.9	57.8 ± 5.4	94%
Placebo + PUVA	22		65.4 ± 4.1	19.9 ± 1.6	97.2 ± 12.2	80%
Etretinate + PUVA	23		57.8 ± 4.4	16.9 ± 1.6	73.7 ± 10.5	80%
Tanew *et al.*,[56]						
Acitretin + PUVA	30	–	40.2 ± 4.6	15.3 ± 1.9	58.7 ± 17.9	96%
PUVA	30	–	51.0 ± 4.7	21.4 ± 2.1	101.5 ± 15.8	80%
Sommerburg *et al.*,[57]						
Acitretin + PUVA	40	8 weeks	44.8 ± 2.5	19.6 ± 0.9	77.6 ± 9.2	70%
Placebo + PUVA	43		43.2 ± 2.2	19.4 ± 1.1	73.0 ± 7.2	44%
Combination with BBUVB						
Iest and Boer,[58]						
Acitretin + BBUVB	9	Max 30 UV	–	19.3 ± 3.7	8.4 ± 3.7	89%
BBUVB	32	Exposure	–	24.9 ± 5.8	11.1 ± 6.4	62.5%
Ruzicka *et al.*,[59]						
Acitretin + BBUVB	40	8 weeks	48.0 ± 12.1	–	8.8 ± 6.8	60%
BBUVB	38		43.3 ± 15.3	–	6.4 ± 5.2	24%
Combination with NBUVB						
Kampitak *et al.*,[60]						
Acitretin + NBUVB	9	Retrospective analysis	Shorter duration of therapy in combination group	Lesser no. of treatments in combination group	Lower cumulative dose in combination group	Marked improvement in combination group
NBUVB	20					
Spuls *et al.*,[61]						
Acitretin + NBUVB (retrospective data analysis)	40	–	–	–	–	72.5% achieved PASI 75
Comparison of combination with NBUVB and PUVA						
Ozdeimer *et al.*,[62]						
Acitretin + NBUVB	30	8 weeks	–	20.7 ± 5.1	13.7 ± 4.4	56.6%
Acitretin + PUVA	30		–	20.4 ± 6.5	38.4 ± 14.1	66.6%

BB, broadband; NB, narrowband; PUVA, psoralen + ultraviolet A; UV, ultraviolet.

similar results in terms of enhanced efficacy, lower numbers of irradiation, final doses, and cumulative doses of NB-UVB required to achieve clearance in the combination group.[60] The combination was well tolerated. The combination of acitretin with NB-UVB results in faster improvement even in more difficult-to-treat patients.[61] The combination is a potent therapeutic regimen for the treatment of severe pustular psoriasis of von Zumbusch type in childhood.[46] Ozdemir *et al.*[62] in a randomized comparison of acitretin–NBUVB phototherapy and acitretin–PUVA combination therapy for psoriasis found both to be equally effective. The combination of acitretin and photo (chemo)therapy is thus more effective, better tolerated, convenient, less costly, and, perhaps, safer during long-term treatment than photo(chemo)therapy or acitretin monotherapy alone. In patients with suboptimal responses to initial acitretin monotherapy, acitretin dose should be reduced before introducing UVB or PUVA, to minimize erythema caused by acitretin-induced thinning of the stratum corneum. In patients with suboptimal responses to UVB or PUVA monotherapy, phototherapy dose should be reduced by 50% before introducing acitretin. Once the disease is controlled, either acitretin or phototherapy can be used for maintenance.[67]

Combination with biologics

Biologics have revolutionized the treatment of psoriasis. However, cost and lack of long-term safety data are two important limitations with biologics. Acitretin, which is a time-tested drug, still holds its important niche in the therapeutic armamentarium of psoriasis, in the era of biologics. Recently it has been used in combination with biologics with good results (Table 6).[30,68–71] Acitretin serves to reduce the dose requirement, increase efficacy,

Table 6 Studies on combination of acitretin and biologics

Drug combination	Study	Dose regimen	Results
Acitretin + biologics	Conley *et al.*,[68]	6 patients got etanercept + acitretin One patient each got adalimumab and alefacept with acitretin	Combination therapy led to enhanced disease control and insignificant adverse effects
Acitretin + infliximab	Takahashi *et al.*,[30]	Four erythrodermic psoriasis patients got infliximab (5 mg/kg) at 0, 2, and 6 weeks and acitretin (0.3–0.6 mg/kg/day)	Excellent outcome at 6 weeks
Acitretin + etanercept	Gisondi *et al.*,[69]	Three groups of severe psoriasis patients received either acitretin alone (0.4 mg/kg) or etanercept alone (25 mg twice weekly s.c.) or combination of etanercept (25 mg once weekly s.c.) and acitretin (0.4 mg/kg daily)	Combined therapeutic regimen was as effective as etanercept 25 mg twice weekly, and more effective than acitretin alone
Acitretin + etanercept	Smith *et al.*,[70]	Fifteen patients with severe recalcitrant psoriasis received combination	Marked improvement in psoriasis area and severity index score. One patient developed non-Hodgkin's lymphoma after 3 years.
Acitretin + adalimumab	Philipp *et al.*,[71]	Four severe or recalcitrant psoriasis patients received combination for mean period of 12.9 ± 12.4 months	Combination safe and effective

and provide protection against the side effects of biologics. As compared to other systemic therapies, it barely affects the immune system and therefore is a suitable candidate for combination treatment with biologics as there will be no additional immune suppression. The combination of biologics and acitretin has a synergistic effect, targeting both the immune and hyperproliferative aspects of psoriasis without increasing the risk of toxicity significantly. In a 24-week, randomized, controlled, investigator-blinded study involving 60 adult patients with moderate to severe chronic plaque psoriasis, the combination therapy (acitretin 0.4 mg/kg per day plus etanercept 25 mg once weekly) was as effective as etanercept 25 mg twice weekly and more effective than acitretin alone.[69] So, acitretin has a dose-sparing effect on biologics, and the combination can significantly reduce the cost of treatment.

One case series described eight patients who had been treated with topical as well as systemic agents, including acitretin.[68] Six of the eight patients received treatment with etanercept (25–50 mg once to twice a week) and acitretin (25–50 mg every other day to daily). The other two patients in the series received acitretin in combination with alefacept and adalimumab each. The combination therapy led to enhanced disease control and other than mild transient cholesterol elevation in one patient, no other adverse effect was noted. Marked improvement and reduction of psoriasis area and severity index (PASI) score was seen in 15 patients with severe recalcitrant psoriasis treated with etanercept in combination with acitretin[70]; three patients developed squamous cell carcinoma while on combination therapy, but all patients had a previous history of squamous cell carcinoma. One patient developed non-Hodgkins lymphoma after three years of etanercept and acitretin.

Therefore, acitretin combined with biologic agents offers a promising method of managing refractory psoriasis.

Rotational and sequential therapy with acitretin

Acitretin has been used as part of rotational therapy in which patients are moved from one monotherapy agent to another to minimize cumulative dose and forestall toxicities.[72] While transitioning from one agent to another, the two may be given in combination for a brief overlap period.

Another way to combine the two drugs is sequential therapy. It was proposed by Koo as a strategy designed to optimize initial efficacy followed by a safe maintenance regimen by the use of specific combination in a deliberate sequence.[73] Sequential therapy is based on the fact that some drugs produce rapid clearing of psoriatic lesions whereas others are better suited for maintenance therapy. Acitretin as monotherapy is more suitable for long-term maintenance therapy as it acts slowly, while there is insignificant cumulative dose toxicity when given for long periods. With continued treatment, patients also develop tolerance to more common mucocutaneous side effects. MTX and CYC act fast and are more useful for initial disease control, but they have cumulative toxicity and, therefore, cannot be used for long periods. Acitretin can be used as a maintenance agent after initial disease control with MTX or CYC. This limits the possible increased side effects when acitretin is used simultaneously with these two drugs. While transitioning between the two drugs, a brief overlap period is required.

Acitretin as monotherapy for initial disease control can be used in GPP, erythrodermic psoriasis, and PPP, and in chronic plaque psoriasis it can be used as re-PUVA. Induction of remission by re-PUVA followed by maintenance with acitretin alone or PUVA alone is another widely used sequential therapy. Table 7 summarizes the results of various studies of acitretin and provides general guidelines for its effective and safe use.

Table 7 Summary of acitretin use in psoriasis

1	Whether given as monotherapy or as combination therapy, dose escalation is the optimal strategy in an individual patient as it allows development of tolerance to side effects.
2	Start with lower doses of acitretin (10–25 mg/day). Gradual escalation every 2 weeks while monitoring for side effects. Optimal dose for monotherapy is 0.3–0.5 mg/kg/day.
3	Improvement occurs gradually, requiring up to 3–6 months for peak response with monotherapy.
4	Overall rate of complete remission is generally <50% with monotherapy. Best response is seen in stable, thin, small plaque-type psoriasis.
5	Higher doses (50–75 mg/day) result in more rapid and possibly more complete response but are associated with significantly increased side effects resulting in poor compliance.
6	Acitretin monotherapy can be considered first-line treatment for PPP, GPP, and erythrodermic psoriasis provided the flare is not life threatening.
7	Combination regimens with topical therapies, other systemic drugs, and photo(chemo)therapy are generally preferred for plaque-type psoriasis and nail psoriasis.
8	Acitretin is a good choice in immunosuppressed individuals (HIV positive or other cause) and those affected with chronic viral hepatitis.
9	Acitretin works well in combination with biologics – increases efficacy and dose-sparing effect, and reduces side effects.

GPP, generalized pustular psoriasis; PPP, palmoplantar pustular psoriasis.

Side effects

Side effects are common and dose limiting, but they can be minimized by appropriate patient selection, careful dosing, and monitoring (Table 8). The adverse effect profile of acitretin is closely related to hypervitaminosis A. Adverse effects are usually mild and reversible in nature and rarely severe enough to require discontinuation of therapy. A higher frequency of adverse effects is seen with higher doses.

Mucocutaneous side effects are the most common side effects and occur in almost all patients to varying degrees (Table 8). In some patients, there is apparent worsening of erythema and plaque expansion occurring shortly after starting the therapy; these patients should be reassured that in most cases it is transient and their psoriasis will improve with continued acitretin therapy. Treatment consists of moisturizing with bland emollients and mild topical corticosteroids. Rarely there is a need for decreasing the dose of acitretin. Adverse effects on nails (Table 8) are relatively less common, and rarely subungual hemorrhages have been reported.[74] Mucocutaneous adverse effects are reversible in nature and improve on stopping of therapy.

Acitretin is a pregnancy category X drug. Major human fetal abnormalities associated with retinoids include meningomyelocele, meningoencephalocele, multiple bony malformations, facial dysmorphia, low-set ears, high palate, anophthalmia, abnormalities of appendages including syndactyly and absence of terminal phalanges, malformations of the hip, multiple synostosis, decreased cranial volume alterations, and cardiovascular malformations.[75] To date, of six known fetal outcomes associated with acitretin use during pregnancy, two had malformations consistent with retinoid embryopathy. Available data do not suggest any safety risk with a male partner taking acitretin at the time

Table 8 Side effects of acitretin and their management

Body organ	Side effects	Management
Mucocutaneous	Cheilitis, rhinitis, dry mouth; xerosis, pruritus, sticky skin and retinoid dermatitis; alopecia, hair pigmentation and curling; paronychia, onychorrhexis, onychoschizia, periungual pyogenic granuloma	Usually mild, reversible, dose related, emollients, topical steroids
Liver	Hepatitis (idiosyncratic or pharmacologic)	Dose reduction or discontinuation
Metabolic	Hypertriglyceridemia and less commonly hypercholesterolemia	Dietary changes, exercise, antilipidemic drugs
Central nervous system	Headache, pseudotumor cerebri	Stop acitretin when suspected, refer to ophthalmologist
Ocular	Xerophthalmia, night blindness	
Musculoskeletal	DISH, bone remodeling abnormalities, ligament calcifications	Close monitoring in those at risk as these side effects usually irreversible
Gastrointestinal tract	Nausea, abdominal pain	Dose reduction
Teratogenic	Meningomyelocele, bony malformations facial dysmorphia, low-set ears, high palate, anophthalmia	Contraindicated in pregnancy
Rare	Peripheral edema, suicidal tendency, capillary leak syndrome	

DISH, diffuse idiopathic skeletal hyperostosis (syndrome).

of conception.[76] At present the FDA has not mandated preventing semen exposure in women of childbearing potential from male patients taking acitretin. Current guidelines recommend that female patients should refrain from ethanol ingestion both during treatment and for a further two months after discontinuing acitretin to avoid conversion to etretinate, which has a longer half-life of elimination. Women of childbearing potential are also advised to use reliable contraception (usually two forms of birth control) during treatment and for at least three years after cessation of therapy.

Retinoid therapy causes hyperlipidemia in 25–40% of patients, which is proportional to the dose.[77,78] It more commonly leads to hypertriglyceridemia than hypercholesterolemia. Hyperlipidemia can be managed with reduction in dietary fat intake and increasing exercise. For hypercholesterolemia that does not adequately respond to lifestyle changes, a lipid-lowering agent such as atorvastatin (10–20 mg/day) may be indicated. Patients with hypertriglyceridemia who do not respond to dietary changes and physical activities may require therapy with gemfibrozil (600 mg twice daily). If triglycerides are >499 mg/dl, the retinoid dose should be decreased by 50%. If triglycerides are >800 mg/dl, the retinoid should be discontinued.[63] Retinoid therapy can be reinitiated once hypertriglyceridemia is under control. Omega-3-acid ethyl esters (P-OM3) may be a useful adjunct for patients with refractory hyperlipidemia.[79] Predisposing factors for hyperlipidemia are obesity, alcoholism, nicotine abuse, diabetes mellitus, familial hyperlipidemias, and use of beta blockers, thiazides, and contraceptives. Lipid levels normalize in most patients after discontinuation of retinoid therapy. Because of the association of psoriasis with metabolic syndrome, monitoring for lipid profile should be more stringent in patients with psoriasis receiving acitretin.

Musculoskeletal side effects, though uncommon, are the only significant adverse effects that are noted with cumulative long-term systemic retinoid therapy and are irreversible even on discontinuing the drug. There are reports of premature fusion of epiphyses, diffuse idiopathic skeletal hyperostosis syndrome, calcification of ligaments, osteoporosis, as well as modeling abnormalities of long bones, occurring in patients on long-term etretinate treatment.[42,80] One prospective study showed that retinoids are likely to cause worsening of pre-existing skeletal overgrowth rather than *de novo* changes.[81]

A chart review of patients who had been on acitretin for more than one year revealed no x-ray-confirmed cases of diffuse idiopathic skeletal hyperostosis syndrome.[82] In a recent prospective study of 51 patients treated with acitretin for two years (average dose 0.5 mg/kgper day), two patients developed unusual skeletal calcifications located in the forearms and hip.[83] In another prospective study, no association was found between daily dose of acitretin, total dose administered, overall duration of treatment, and risk of osteopenia or osteoporosis.[84] If bone abnormalities occur, they do not resolve on discontinuation of treatment. Thus, the literature reveals conflicting reports on skeletal toxicity of acitretin. A single radiograph of the ankle, being the most common site of involvement, should be done before the start of high-dose/long-term acitretin therapy and yearly thereafter. In children, growth monitoring should be done in addition.

Use of acitretin may cause elevations in serum liver enzymes in up to 15% of the patients.[67,78] These increases, however, are often transient, more common with high doses, and are reversible upon lowering the acitretin dose or discontinuing therapy. Oral retinoids may be hepatotoxic with two types identified: pseudoallergic (idiosyncratic) hepatitis or low-grade (pharmacologic) hepatotoxicity.[85] The increase in liver enzymes usually begins 2-8 weeks after the start of treatment. Alcoholics, diabetics, and obese individuals are at increased risk for hepatotoxicity and require more frequent liver function monitoring during acitretin treatment.

Pseudotumor cerebri, or benign intracranial hypertension, has occurred in very rare cases with acitretin therapy. There is a lack of evidence-based data to support the claim that acitretin definitely causes pseudotumor cerebri.[86] Patients should be counseled for signs and symptoms of pseudotumor cerebri (severe headaches, nausea, emesis, visual changes). Ophthalmologic evaluation to rule out papilledema is warranted if pseudotumor cerebri is suspected. Retinoid treatment should be discontinued, and the patient should be referred for appropriate care. Oral retinoids should not be taken in combination with tetracycline class antibiotics.

There is no scientific evidence base for depression as a side effect of acitretin, and it is more of a theoretical concern/class labeling.[86,87] Other rare side effects that have been reported include arthralgia and myalgia,[88,89] peripheral edema,[90] suicidal tendency,[91] and maculopathy,[92] capillary leak syndrome,[93] granulation tissue in palpebral conjunctiva,[94] hair pigmentation, and curling.[95] Acitretin has significant drug interactions (Table 9), and combination with these drugs should be avoided to prevent untoward side effects. Table 10 enumerates the general instructions to be given to every patient who is started on acitretin.

Conclusions

Acitretin is a safe and effective treatment for psoriasis both as monotherapy and as combination therapy. It is highly effective in pustular psoriasis and erythrodermic

Table 9 Important drug interactions of acitretin

Drugs	Interaction
Alcohol	Acitretin converted to etretinate
Methotrexate	Cumulative hepatotoxicity, caution in combination therapy
Vitamin A	Hypervitaminosis A
Microdosed progestin minipill	Reduce its effect
Phenytoin	Acitretin reduces its protein binding
Tetracyclines	Raised intracranial pressure

Table 10 General instructions for patients started on acitretin[41]

Avoid excessive sun exposure
Do not donate blood during therapy and 1 year after stopping acitretin
Exercise and avoid high-fat diet
Refrain from waxing for hair removal
Avoid concomitant medication (Table 9)
Do not exceed recommended daily intake of vitamin A (2400–3000 IU/day)
Strict compliance with contraception
Abstain from alcohol intake
More frequent monitoring of blood glucose during early treatment in those on antidiabetic medication

psoriasis and moderately effective as monotherapy in plaque-type psoriasis. Acitretin is an ideal agent for use in combination therapy by means of enhancing the effects of other medications while reducing their toxicity besides its inherent chemoprotective effect. It is better avoided as the initial treatment choice in unstable psoriasis and predominant flexural psoriasis. Dose should be titrated to minimize side effects. While low-dose treatment may not be as quick to produce treatment success as high-dose treatment, it minimizes side effects and leads to greater patient compliance and efficacy over an extended period. Patient counseling, including discussion of patient expectations, should be incorporated as part of the treatment plan whenever acitretin is introduced as a therapeutic option. Acitretin is certainly an underused and seemingly considered as a less favorable drug in developing countries due to many reasons such as lack of long-term experience of its use, limited availability, poor patient compliance due to cost, and slow clinical response as compared to other cheaper agents such as methotrexate. Besides, acitretin works well in a specific subset of patients with psoriasis, and therefore patient selection has to be appropriate lest poor efficacy and side effects would forestall its further use. By virtue of its mechanism of action and lack of immunosuppressive side effects, acitretin has a pivotal place in the therapeutic armamentarium of psoriasis to which patients should not be denied.

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