British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology

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Acitretin, a synthetic retinoid, is the pharmacologically active metabolite of etretinate. It replaced etretinate in the late 1980s because of its more favourable pharmacokinetic profile, and it is an established systemic second-line therapy for severe psoriasis resistant to topical therapy. Bioavailability is enhanced by food, especially fatty food.[1] Acitretin is 50 times less lipophilic than etretinate and has a shorter elimination half-life. However, there is evidence that small amounts of acitretin are re-esterified to etretinate, which has a very long half-life, especially in the presence of alcohol.[2,3] Intracellularly, it interacts with cytosolic proteins and nuclear receptors, which are part of the steroid-thyroid hormone superfamily. We know that these nuclear receptors act as transcriptional factors for specific DNA sequences; however, their role in the retinoid pathway is largely unknown. In psoriasis and other disorders of keratinization, acitretin normalizes epidermal cell proliferation, differentiation and cornification.[4,5] It is thought to exert these effects by interfering with the expression of epidermal growth factor genes. There is also evidence that acitretin has immunomodulatory properties by inhibiting dermal microvascular endothelial cells[6] and neutrophil migration.[7,8] Acitretin is licensed for use in severe extensive psoriasis which is resistant to other forms of therapy, including topical, light and systemic; palmoplantar pustular psoriasis; severe Darier disease (keratosis follicularis) and severe congenital ichthyosis.

It is highly teratogenic and must not be used by women who are pregnant or are planning a pregnancy. Acitretin is highly bound to plasma protein and metabolized in the liver. It is excreted to an equal extent by renal and hepatic routes.

Although available for 20 years there have not been any published guidelines on the use of acitretin. Its clinical use is almost completely restricted to dermatology and it has important metabolic, skeletal and teratogenic side-effects. We felt it important to produce evidence-based guidelines on its use in dermatology.

Materials and methods

A scoping meeting decided that the guideline would include only evidence pertaining to acitretin and would not make direct inferences from studies of the parent drug etretinate. The target audience for the guideline is dermatologists.

Inclusion criteria

We included all randomized controlled trials (RCTs) testing acitretin but also needed to survey the literature on monitoring patients taking acitretin and adverse effects which could include well-designed cohort or case–control analytical studies and, for rare but significant side-effects, case reports.

We included in the search papers written in English, French, Spanish, Italian and German, and those describing adverse drug reactions, clinical monitoring and consensus statements from respected authorities based on clinical experience and consensus committees.

The following databases were searched: EMBASE, MEDLINE, CINAHL, PubMed, The Cochrane Library, RCP Guidelines Database, DARE; this gave 1325 hits. These abstracts were reviewed and, after sifting, 316 papers were reviewed by the authors. The search strategy is available separately online (see Data S1).

Stakeholder involvement and peer review

The draft guideline was made available for consultation and review by the BAD membership. The final document was peer-reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines and Audit & Clinical Standards Subcommittees) prior to publication.

Indications and efficacy: review of the evidence

Psoriasis

We found four RCTs comparing acitretin with placebo[9–12] and four RCTs comparing acitretin with etretinate,[13–16] with one open study.[17] The types of disease in these trials and the results are heterogeneous and include generalized pustular, severe and erythrodermic variants. Acitretin is effective compared with placebo but many of these studies are poorly reported or dose ranging with small numbers in each dosage group. Higher doses of acitretin (50–75 mg daily) are more effective than low doses in these RCTs,[9–11] with lower doses of 10–25 mg daily not significantly better than placebo,[9,11,14] although one trial established efficacy at 25 mg daily.[10] Taken together, the randomized period of these studies is short, and longer-term open extensions with variable doses titrated to the patients' needs suggest greater efficacy over time with reduction in area and increasing percentage of patients cleared between 20 and 52 weeks.[12,17] Twelve-week studies are likely to underestimate the efficacy of acitretin and optimal response will be seen at 12 weeks or later with 70% showing marked improvement at 1 year in the open study.[17] Typically 75% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 75) was seen at 12 weeks.[13] However, only 2–10% cleared completely.

In the comparative studies with etretinate there was a trend for acitretin to be slightly less effective and to present a higher incidence of similar side-effects. In an 8-week trial in 175 patients acitretin at 10, 25 and 50 mg daily produced a 50% improvement in psoriasis in 50%, 40·5% and 54%, respectively, compared with 61% with etretinate.[14] Anecdotal reports also suggest a differential response.[18] Side-effects, like efficacy, were dose related.

Pearce *et al.*[19] reanalysed retrospectively the pivotal phase three trials and found that common adverse events were two to three times more frequent in patients receiving 50 mg daily compared with patients receiving 25 mg daily. On 25 mg daily changes in liver enzymes and lipids were minimal compared with higher doses. The authors advocated use of a low dose as high doses are limited due to adverse events. Others have advocated gradual dose escalation as optimal.[20]

All studies preceded the now standardized proportion achieving PASI 75 outcome measure. However, 23% of 112 patients achieved 75% improvement in one typical study.[14] In one study 90% improvement was achieved by 10% of patients.[15] A retrospective *post hoc* analysis of the data from three studies was published using the now more widely accepted criteria of the proportion of patients achieving at least 50% improvement in PASI (PASI 50) and at least 75% improvement (PASI 75).[21] This showed 52% achieving PASI 75 and 85% achieving PASI 50 after 12 weeks in the multi-centre Nordic trial on a median dose of acitretin 40 mg daily.[13] This was a per protocol analysis. In the Canadian open trial[17] patients started on acitretin 50 mg daily and were tapered to a mean of 40 mg daily. A total of 46% achieved a PASI 75 response and 76% a PASI 50 response by the end of treatment (intent to treat analysis, average duration 267 days).

There is an impression from retrospective anecdotal studies that acitretin is more effective in erythrodermic[22] and pustular psoriasis than in chronic plaque psoriasis.[23] Etretinate was the most effective agent in one study of pustular psoriasis.[24]

In an open study of 396 patients with nail psoriasis who received acitretin in doses of 0·2–0·3 mg kg^{-1} daily for 6 months, the mean improvement in Nail Psoriasis Severity Index was 41% and 25% of patients cleared or almost cleared.[25]

Combination therapy in psoriasis

Acitretin and PUVA

Four RCTs compared acitretin and PUVA (rePUVA) with placebo and PUVA, or additionally etretinate and PUVA in two.[26–28] These show the acitretin-PUVA combination to be more effective than PUVA alone, reducing the number of PUVA treatments, exposure to ultraviolet (UV) A and the clinical scores, and to be as effective as etretinate-PUVA combination. A trend was seen towards a higher incidence of side-effects in the acitretin-treated patients.[28] In considering the preventive action of acitretin against carcinogenesis and the concerns relating to the carcinogenicity of PUVA therapy there are theoretical advantages to this combination which help mitigate the more serious side-effects of PUVA. This is supported for etretinate in the American PUVA cohort[29] where the incidence of squamous cell carcinomas was reduced by

retinoids. The same could be said for narrowband UVB where the carcinogenic risk is probably less.

Acitretin and ultraviolet B

One RCT, two open studies and one retrospective study compared acitretin in combination with UVB[24,30–33] with UVB alone. Better outcomes and sparing of UVB were consistently seen with acitretin-UVB in combination than with UVB alone. In a recent RCT acitretin and UVB (TL-01) cleared 55·6% of patients compared with 63·3% treated with acitretin and PUVA.[34]

Acitretin and calcipotriol ointment

Two large RCTs combining acitretin with calcipotriol ointment showed additive benefits of the combination although each relied on subjective outcome measures.[35] In one study the number of patients clear or almost clear was increased from 41% to 67% by the addition of calcipotriol[36] and the number of patients with complete clearance increased in the other from 15% to 40% after 12 weeks.[37]

Other combinations

Acitretin with hydroxycarbamide and with etanercept have anecdotally been effective for some patients with plaque psoriasis.[38] The combination of methotrexate and acitretin has been used in patients with severe psoriasis, where all other treatments have failed.[39,40] This has been based on anecdotal evidence extrapolated from etretinate.[41] Although this combination can be very effective, sporadic severe hepatotoxic responses have been reported.[42–44] The efficacy of concomitant use of acitretin with ciclosporin is not convincing[45] and, in addition, this combination carries the risk of accumulation of ciclosporin as both drugs are inactivated by the same cytochrome P-450 system.[46] A recent RCT showed similar efficacy from the combination regimen of acitretin 0·4 mg kg^{-1} daily and etanercept 25 mg once weekly to that observed with etanercept 25 mg twice weekly. Although a small study, this suggests that the addition of acitretin has an etanercept-sparing effect.[47]

Palmoplantar pustulosis

Two RCTs compared acitretin with placebo in palmoplantar pustulosis.[48,49] Acitretin was significantly more effective than placebo, acting within 4 weeks to produce a fivefold reduction in pustules. After 12 weeks the second study[49] comparing acitretin and etretinate showed a tenfold reduction in pustules which was similar for both retinoids.

Prevention of malignancy

There have been numerous reports of retinoids used as prophylaxis against skin cancer in organ transplant recipients. Three RCTs were systematically reviewed in 2005 by Chen *et al.*[50]

These included two parallel studies of 44 and 26 patients followed for 6 and 12 months, and a crossover study of 23 patients. Only the short study had a fixed dose of 30 mg daily. Longer-term studies had differing dose regimens. In the study by George *et al.*[51] acitretin was titrated from 25 mg daily up to 50 mg daily or down to 25 mg on alternate days. In the crossover study there was a 42% decrease in squamous cell carcinoma in the acitretin period compared with drug-free period. A similar trend was seen with basal cell carcinoma although numbers were small. For patients treated for 6 months and off treatment for 6 months, two of 19 patients (11%) in the acitretin group reported a total of two new squamous cell carcinomas during the treatment period, compared with nine of 19 patients (47%) in the placebo group who developed a total of 18 new carcinomas. The two trials counting premalignant lesions showed a significant reduction in these. Keratotic lesions increased by 28% in the placebo group and decreased by 13·4% in the acitretin group.[52] The third study which compared different doses of acitretin did not show a difference in tumour rate between doses of 0·4 mg kg^{-1} daily and 0·4 mg kg^{-1} daily reducing to 0·2 mg kg^{-1} for 9 months, nor a significant reduction compared with that observed in the preceding year without acitretin.[53] However, thickness of lesions was reduced and numbers of actinic keratoses were reduced. Side-effects were a limiting factor in these studies, leading to significant drop-outs, although lower doses were tolerated. Overall these were small studies with a modest reduction in cancer over a short period of observation, and further studies are required.

Other retinoids have anecdotally prevented malignancy in congenital skin cancer syndromes such as xeroderma pigmentosum (isotretinoin)[54] and basal cell naevus syndrome (etretinate)[55,56] and it may be implied that acitretin has a place here.

Congenital ichthyoses and keratoderma

Acitretin has been used in severe forms of the heterogeneous group of the ichthyoses where marked hyperkeratosis is the main pathological component. The evidence for its efficacy is based on anecdotal reports. We found five open series, one of which was prospective, describing its use in the ichthyoses.[57–60] In one, 29 children had conditions including lamellar ichthyosis (9), nonbullous ichthyosiform erythroderma (5), one of whom responded poorly, bullous ichthyosiform erythroderma (4) and Sjögren-Larsson syndrome (3).[57] A patient with Netherton syndrome experienced marked worsening. In another study, 33 patients (21 adults and 12 children) with ichthyoses, palmoplantar hyperkeratosis or Darier disease were treated for a period of 4 months. Most patients showed marked improvement or remission. The results in congenital ichthyosiform erythroderma, lamellar ichthyosis and Papillon-Lefèvre syndrome were judged by the authors empirically as better than those usually reported with etretinate.[59] Milder ichthyoses such as ichthyosis vulgaris and X-linked recessive ichthyosis should not require acitretin therapy.[61] However, six patients with severe X-linked recessive ichthyosis were successfully treated.[62]

Among the keratodermas, Vohwinkel syndrome (keratoderma mutilans with hearing loss), keratitis-ichthyosis-deafness (KID) syndrome,[63] hereditary punctate palmoplantar keratoderma,[64] type I hereditary punctate keratoderma,[65] epidermolytic hyperkeratosis (a rare form of ichthyosis sometimes associated with palmoplantar keratoderma)[66] and Papillon-Lefèvre syndrome[67,68] have all been recently reported as successfully treated with acitretin in small series. Treatment of epidermolytic palmoplantar keratoderma may result in large erosions.[61]

Darier disease

In one RCT, Christopherson *et al.*[69] compared acitretin with etretinate in 26 patients and found similar rates of marked improvement or remission in both groups, with 10 of 13 patients responding. An open study of five patients[70] showed marked improvement to complete clearance in four. This group found that 10–25 mg daily was sufficient, and lower doses were required in Darier disease than other diseases. This is reflected in the licence. In an open study of 13 patients,[71] three patients cleared and seven improved markedly on 30 mg daily, followed by dose reduction.

Pityriasis rubra pilaris

A single retrospective study of 14 patients, of whom nine were treated with either etretinate or acitretin 0·5 mg kg^{-1} daily for an average period of 18·8 months, achieved partial or complete clearing in seven without major side-effects. Five patients responded to methotrexate 15–25 mg daily but other treatments, including steroids and PUVA, were inconsistent.[72] Although anecdotal, the authors considered retinoids to be the first-line treatment for pityriasis rubra pilaris.

Lichen planus

In one RCT in severe lichen planus (LP), Laurberg *et al.*[73] showed marked improvement in 64% of patients on acitretin 30 mg daily vs. 13% on placebo. In an open 8-week extension, 83% of the placebo patients responded. A total of 17 of 23 patients with associated mucocutaneous disease improved significantly on acitretin. In a meta-analysis, Cribier *et al.*[74] included five open studies with 58 patients with oral LP treated with etretinate (mostly poor-quality studies), and one crossover RCT with 28 patients which showed significant improvement with etretinate over placebo. Etretinate was the favoured retinoid therapy. The authors recommend acitretin as first-line therapy in cutaneous LP and give further anecdotal evidence. Acitretin may also be preferred in the hyperkeratotic variant of LP for its modulating effect on keratinization.

Lupus erythematosus

In an RCT of 58 patients[75] comparing acitretin 50 mg daily for 8 weeks with hydroxychloroquine 400 mg daily, improvement was found in 46% and 50%, respectively, but four

patients had to stop acitretin because of side-effects which were more frequent in this group. In one open trial of 20 subjects,[76] the result was unsatisfactory in five. In 15 patients, total clearing or marked reduction of all lesions was seen. Acitretin was superior to previous therapy with antimalarials and/or systemic corticosteroids in seven, and five of six patients with subacute cutaneous lupus erythematosus showed complete clearing of their lesions within 2–4 weeks. As in LP, a verrucous variant is seen where the modulation of hyperkeratosis may be an advantage favouring acitretin.

Lichen sclerosus

One RCT randomized 78 patients but only measured efficacy per protocol in 46 subjects. A total of 14 of 22 patients on acitretin responded compared with six of 24 in the placebo group.[77] However, due to the high drop-out rate the study has a high risk of bias (1−; see Appendix 1) and could not be used to make a recommendation.

Other conditions

A 51% reduction in hyperkeratotic hand eczema was seen in one RCT of 29 patients.[78] In one study of mycosis fungoides, PUVA in combination with interferon alfa-2a was superior to acitretin with interferon.[79] The evidence for the use of acitretin for the treatment of warts is sparse and insufficient to base a recommendation. An open study of etretinate in children with severe warts showed clearance in 16 of 20 patients and in four there was improvement then relapse on stopping therapy.[80] However, in this age group warts often clear spontaneously. There are a few case reports of warts clearing with acitretin,[81,82] but in one of these the warts only improved in bulk and recurred on stopping therapy.[82] Acitretin has been used anecdotally as an adjunct to therapy in giant condyloma acuminatum[83] but in this case response was arguably related to excision and imiquimod used in combination. In epidermodysplasia verruciformis acitretin has been suggested as an adjunct in combination with interferon alfa-2a[84] but as monotherapy was ineffective.[85]

Safety and side-effects

Side-effects are seen in most patients receiving acitretin. However, they usually disappear when the dosage is reduced or the medicine is withdrawn. An initial worsening of psoriasis symptoms is sometimes seen at the beginning of the treatment period.

Teratogenicity

Acitretin is teratogenic regardless of the duration of treatment or dosage used. Although since the marketing of acitretin only one report of human teratogenicity associated with acitretin has been published, acitretin is converted to etretinate, which has a much longer half-life and has been associated with sev-

eral cases of retinoid-induced embryopathy.[86–88] Potential teratogenic effects associated with retinoids are characteristic of those associated with hypervitaminosis A.[89,90] Retinoid embryopathy can result in craniofacial dysmorphias such as high palate and anophthalmia, abnormalities of appendages including syndactyly and absence of terminal phalanges, malformations of the hip, meningoencephalocele, and multiple synostosis.[89–92] The teratogenic risk is particularly high for women exposed to treatment during the first trimester of pregnancy. Available data do not appear to indicate any reproductive safety risks due to paternal treatment with acitretin.[93]

Mucocutaneous effects

The most frequent side-effect is dryness of the lips, which can be alleviated by application of a fatty ointment such as Vaseline® (Unilever, Walton-on-Thames, U.K.). Mucous membranes and transitional epithelia become dried out or exhibit inflammatory lesions. This can occasionally lead to nose bleeds and rhinitis, and to ocular disturbances including photophobia, xerophthalmia and conjunctivitis sometimes resulting in intolerance of contact lenses. Cheilitis, dry mouth and thirst may also occur. Occasionally stomatitis, gingivitis and taste disturbances have been reported.

Thinning, redness and scaling of the skin may occur all over the body, particularly on the palms and soles. For many patients the increased sensitivity and fragility of the skin make walking and grasping objects difficult.

Increased hair loss, nail fragility and paronychia are sometimes observed. Hair loss can occur in up to 75% of patients, but frank alopecia is observed in < 10% of treated patients. Periungual pyogenic granuloma may occur after long-term acitretin therapy. Occasionally bullous eruption and abnormal hair texture have been reported.

Rarely, patients may experience photosensitivity reactions.

Another side-effect is the initial aggravation of psoriasis, which is sometimes seen during the first 4 weeks of treatment. A 'retinoid dermatitis', which may resemble unstable psoriasis, can also develop in up to 25% of patients receiving high-dose oral acitretin.[13,94,95] The severity of mucocutaneous side-effects was found to be dose related in some studies, with a higher incidence at doses of 50–75 mg daily.[13,94,95] However, this was not found to be the case in other studies.[9,14]

If severe mucocutaneous reactions occur during effective therapy with acitretin, dose reduction should be attempted before discontinuing the drug.

Hepatotoxicity

Transient, usually reversible, elevation of liver enzymes may occur in up to 15% of patients receiving acitretin.[22,90]

Severe hepatotoxic reactions resulting from retinoid use are rare, and reports include a severe cholestatic hepatitis occurring in a patient with a hypoplastic kidney,[11,96] and a severe hepatotoxic reaction with progression to liver cirrhosis.[90,97,98] However, data from 1877 patients receiving acitretin therapy showed overt chemical hepatitis in only 0·26%.[90] A total of 83 patients followed by liver biopsy for 2 years showed no significant hepatotoxicity with acitretin other than mild changes.[97] Alcoholics, diabetics and obese individuals are at increased risk for hepatotoxicity and require more frequent liver function studies.

Hyperlipidaemia

Hyperlipidaemia is proportional to the dose of acitretin and usually reverses within 4–8 weeks after discontinuation.[99] The greatest increase is seen in triglycerides, which occurs in 20–40% of patients, and is associated with the very low density lipoprotein (VLDL) fraction. Hypercholesterolaemia, seen in 10–30% of patients treated with acitretin, relates to increases in both the VLDL and/or low density lipoprotein (LDL) fractions and a parallel decrease in the high density lipoprotein (HDL) fraction.[99] In addition, HDL levels have been found to be decreased in about 40% of patients taking acitretin.[100] The LDL/HDL ratio (atherogenic index) has been directly correlated to the risk of developing cardiovascular disease, and therefore fasting lipids should be regularly checked in all patients receiving treatment with acitretin. Increases of serum triglycerides to levels associated with pancreatitis are not common, although one case of fatal fulminant pancreatitis has been reported.[90]

These changes in the lipid profile are dose related and may be controlled by dietary means (including restriction of alcohol intake) and/or by reduction of dosage of acitretin. A high fish oil diet was found effective in partially reducing hypertriglyceridaemia and increasing HDL cholesterol in patients treated with etretinate and acitretin.[100] Gemfibrozil taken orally is also effective, if required.[101] Hypertriglyceridaemia is likely to occur in patients with predisposing factors such as diabetes mellitus, obesity, increased alcohol intake, or a family history of these conditions.

Skeletal abnormalities

The effects of acitretin on the skeletal system are not yet well documented; however, available data suggest similarities to etretinate.[102,103] Long-term (2–4 years) treatment with etretinate was associated with radiographic evidence of extraspinal tendon and ligament calcification. However, estimates of the incidence vary widely, the most common sites being ankles, pelvis and knees.[104,105] Diffuse idiopathic skeletal hyperostosis (DISH)-like involvement, characterized by degenerative spondylosis, vertebral arthritis, and syndesmophytes of the vertebral spine, has been reported as a side-effect of systemic retinoids. Two long-term retrospective studies involved repeated radiological surveys to detect abnormalities but no correlation with dose or duration of treatment has been shown.[105] This study in 135 patients showed no evidence of a link between hyperostosis and prolonged retinoid therapy. A prospective study of 51 patients treated with acitretin over 2 years revealed bone exostoses in only two patients (in the

hip and forearm) that would not have been detected using lateral spine X-rays.[106] A further retrospective study of long-term acitretin revealed no cases of DISH.[107] Regular radiological evaluations have been suggested in the literature but the evidence does not support this practice which exposes subjects to unnecessary radiation; our consensus is that routine radiographic assessments are not required for long-term acitretin therapy. Targeted X-rays for atypical musculoskeletal pain may be informative.

Concern about the use of acitretin in children has arisen from occasional reports of bone changes, including premature epiphyseal closure,[108] skeletal hyperostosis and extraosseous calcification in children on long-term treatment with etretinate.[109] It should be noted that very high dose exposure in one case led to osteopenia and fractures in the bones that fused prematurely and in the other case premature closure was a symptomless observation on X-rays.[108] Five children treated with etretinate had periosteal thickening in the fibula, ulna, metacarpal or metatarsal bones that either developed or progressed on therapy. Compared with age- and sex-matched normal controls, the children had decreased cortical bone thickness of the second left metacarpal bone. However, prospective follow-up of 42 children treated over 11 years did not reveal any abnormalities that would significantly impede starting or continuing therapy.[110] Effects on growth have not subsequently been seen in a further 18 children treated with retinoids at Great Ormond Street Hospital (David Atherton, personal communication).

If, in the opinion of the treating physician, the child's condition is severe enough to be physically, psychologically or socially incapacitating and such therapy is undertaken because the benefits outweigh the risks, then the child should be clinically monitored for any abnormalities of growth parameters and bone development. An appropriate daily dose in children under 12 years of age is 0.5 mg kg^{-1}; occasionally this can be increased up to 1 mg kg^{-1}.

Other rheumatological manifestations that may occur during therapy with acitretin include arthralgias, arthritis, myalgia, and a few cases of vasculitis, Wegener granulomatosis and erythema nodosum. Arthralgia and myalgia represent the most frequent rheumatological sequelae, occurring in up to 25% of patients.[111]

Two previous small studies indicated a possible increased risk of osteoporosis in subjects receiving etretinate and this is a feature of the hypervitaminosis A syndrome;[112,113] however, a further study has refuted this risk[114] and in a prospective study of 30 patients treated for 3.6 years with acitretin, osteoporosis was not detected on DEXA scans.[114]

Other side-effects

Benign intracranial hypertension (pseudotumor cerebri) has occurred in very rare cases with use of systemic retinoids including one instance following acitretin use.[90,115] In some cases with isotretinoin, this effect has been associated with concurrent tetracycline or minocycline administration.[116] Patients with severe headache, nausea, vomiting and visual disturbance should discontinue acitretin immediately and be referred for neurological evaluation.

Blurred or decreased night vision has been reported occasionally.[22]

Nausea has been reported infrequently.[22]

Increased incidence of vulvovaginitis due to *Candida albicans* has been noted during treatment with acitretin.[117]

Retinoids are associated with greater insulin sensitivity and could therefore induce hypoglycaemia in patients on anti-diabetic medications.[118] These patients should be advised to check their capillary glucose levels regularly, perhaps more frequently than usual, in the early stages of treatment.

Acitretin does not significantly affect wound healing. There is some evidence that healing was delayed by retinoids in diabetic rats[119] and that epidermal proliferation was reduced by acitretin in psoriasis.[120] However, in a study of 44 complex wounds in transplant recipients there were no significant effects on wound infection, dehiscence, hypertrophic scarring or hypergranulation. There is therefore no need to stop acitretin for routine surgery such as orthopaedic procedures.[121]

Overdose

Signs and symptoms of overdosage with acitretin would probably be similar to acute vitamin A toxicity and include headache, nausea, vomiting, drowsiness and vertigo. They would be expected to subside on acitretin withdrawal without need for treatment.

Recommendations

See Appendix 1 for definitions of levels of evidence and strengths of recommendation.

In which conditions should acitretin be used?

Acitretin monotherapy is recommended in the treatment of:
1 Severe psoriasis, or psoriasis with severe effects on quality of life, meriting systemic therapy, which is resistant to topical therapy, phototherapy or is unsuitable for these treatments (A, 1+).
1.1 Acitretin is recommended as a combination with PUVA therapy or narrowband phototherapy (A, 1+).
1.2 Acitretin is recommended with hydroxycarbamide (D, 3)
1.3 Acitretin is recommended in combination with calcipotriol ointment (A, 1+).
1.4 The following combinations are not recommended:
　　Acitretin with ciclosporin: no evidence of additive efficacy (D, 3).
　　Acitretin with methotrexate: potential for severe hepatic toxicity (except in exceptional cases) (D, 3).
2 Palmoplantar pustular psoriasis (A, 1+).
3 Hyperkeratotic hand eczema (A, 1+).
4 Severe Darier disease (keratosis follicularis) (A, 1+).
5 Severe congenital ichthyosis (D, 3).
6 Keratoderma (D, 3).
There is evidence that the following conditions benefit from acitretin's antimitotic and keratolytic actions:
1 Lichen planus (A, 1+)

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2 Lichen sclerosus (A, 1+)
3 Discoid lupus erythematosus (A, 1+)
4 Prevention of cutaneous malignancies in organ transplant patients (A, 1+).

What are the contraindications to acitretin therapy?

1 Acitretin therapy is contraindicated in pregnancy and breast-feeding.
2 Acitretin therapy in the above indications should be avoided in women of childbearing potential where there is a suitable alternative.

What precautions should be taken when acitretin is prescribed for women of childbearing age?

- Strict contraception is practised 4 weeks before, during and for 3 years after treatment.
- Pregnancy has been excluded by a medically supervised negative pregnancy test within 2 weeks prior to therapy.
- Therapy should start on the second or third day of the next menstrual cycle.
- The treating physician must explain clearly and in detail what precautions must be taken. This should include the risk involved and the possible consequences of pregnancy occurring during acitretin treatment or in the 3 years following its cessation.
- The patient must be reliable and capable of understanding the risk and complying with effective contraception, and confirms that she has understood the warnings.
- The patient should be advised to abstain from alcohol which increases the metabolism of acitretin to etretinate.
- Acitretin therapy should be avoided in the presence of significant hepatic impairment (enzymes > 2 times normal), hepatitis and alcohol abuse.
- Acitretin therapy should be avoided in moderate to severe renal impairment.

What special precautions should be taken when prescribing acitretin?

- Patients should not donate blood either during or for at least 1 year following discontinuation of therapy.
- 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.[108,122,123] If, in the opinion of the treating physician, the benefits significantly outweigh the risks and such therapy is undertaken, the child should be carefully monitored for any abnormalities of growth parameters and bone development including plotting growth charts.
- The effects of UV radiation are enhanced by retinoid therapy, therefore patients should avoid excessive exposure to sunlight and use of sun lamps.
- Women (and men) should refrain from waxing as a method for hair removal as retinoids cause skin fragility.

- Retinoids are associated with greater insulin sensitivity and could therefore induce hypoglycaemia in patients on antidiabetic medications.[118,124] In this subset of patients, serum glucose levels should be checked more frequently than usual in the early stages of treatment.
- People with diabetes, alcoholism and obesity need to be monitored more frequently as they have an increased risk of hypertriglyceridaemia.
- Advice against exceeding recommended daily intake of vitamin A (2400–3000 IU daily, i.e. 0·8–1 mg daily) should be given.[125]

What drugs can interact with acitretin?

Clinically significant interactions may occur with the following drugs, which should be avoided or used with caution:
- **Methotrexate**
  Increased risk of liver toxicity. Sporadic episodes of toxic hepatitis have been reported following the concomitant use of etretinate and methotrexate.[42,44.]
- **Tetracycline**
  In some cases with other retinoids, benign intracranial hypertension has been associated with concurrent tetracycline or minocycline administration.[90] In the single reported case of pseudotumor cerebri occurring in a patient on acitretin, however, neither tetracycline nor minocycline was involved.[90]
- **Mini-pill**
  Acitretin decreases the anti-ovulatory effect of the progestin-only pill (mini-pill) but has no effect on the combined preparations.[126,127]
- **Phenytoin**
  Acitretin partially reduces the protein binding of phenytoin. The clinical significance of this is as yet unknown.
- **Antidiabetic agents**
  Increased risk of hypoglycaemia.
- **Corticosteroids**
  Increased risk of hyperlipidaemia.
- **Vitamin A**
  Intake should not exceed the recommended dietary allowance (2400–3000 IU daily).

What are the preliminary investigations prior to starting acitretin?

- **Teratogenicity**
  In women of childbearing age pregnancy must be excluded by negative pregnancy test within 2 weeks prior to therapy. Acitretin should be started only on the second or third day of the next menstrual cycle. Effective contraception must be practised for at least 4 weeks before and during therapy with acitretin, and for 3 years after treatment with acitretin has ceased.[128] In the U.S.A. it is recommended that contraception is practised for at least 3 years after discontinuation of acitretin therapy.[129] According to the label in Europe contraception is mandated for at least 2 years after treatment. There are no pharmacokinetic reasons for this discrepancy and the opinion of the guideline development group was to err on the side of caution and to give consistent patient advice. We have therefore recommended continuing contraceptive measures for 3 years.

- **Liver disease**
  Enquire regarding past or current history of liver disease, excess alcohol intake, and hepatotoxic drugs.
  Check alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, bilirubin.
- **Renal disease**
  Enquire regarding past or current history of renal disease, nephrotoxic drugs.
  Check urea, electrolytes and creatinine.
- **Hyperlipidaemia**
  Enquire regarding past or current history of disturbances of lipid metabolism, diabetes mellitus, obesity, alcoholism.
  Check fasting cholesterol, triglycerides.
- **Abnormal glucose tolerance**
  Enquire regarding history of diabetes mellitus, antidiabetic drugs.
  Check fasting glucose.
- **Bone changes**
  The effects of acitretin on the skeletal system are rare; however, available data[130] suggest possible similarities to etretinate. Long-term etretinate and isotretinoin treatment is associated with periosteal thickening, premature epiphyseal closure in children, osteophyte formation, extraspinal tendon and ligament calcification and DISH (diffuse idiopathic skeletal hyperostosis)-like involvement.[104,130] Routine radiography has no place in the monitoring of acitretin therapy and is potentially harmful. Musculoskeletal pain is common and only if atypical would we recommend targeted investigation with X-rays. Children taking acitretin should have their growth charted.

How should acitretin be prescribed?

Therapy should be initiated only under the responsibility of a supervising dermatologist

The capsules should be taken once daily with meals or with milk.[131] Acitretin necessitates individual adjustment of dosage in view of the fact that there is a wide variation in its absorption and rate of metabolism. In addition, both therapeutic and toxic responses to the drug are dose dependent and vary greatly among individual patients. For these reasons the following dosage recommendations can serve only as a guide.

Adults

Effective doses of acitretin as a single agent appear to be in the range of 25–50 mg daily.[20,94] Gradual dose escalation has been shown to be the most effective approach and allows gradual onset of 'tolerance' to side-effects.[94,132] The initial daily dose, 25 mg or 30 mg for 2–4 weeks, may give satisfactory therapeutic results. The maintenance dose must be based on clinical efficacy and tolerability. In general, a daily dose of 25–50 mg taken for a further 6–8 weeks achieves optimal therapeutic results. It may be necessary in some cases to increase the dose up to a maximum of 75 mg daily. Response is gradual and typically requires 3–6 months to reach a peak. Therapy can be discontinued in patients with psoriasis whose lesions have improved sufficiently. Relapses should be treated as described above.

In patients with Darier disease a starting dose of 10 mg daily may be appropriate. Patients with severe congenital ichthyosis and Darier disease are likely to require long-term treatment with acitretin, as are some patients with psoriasis; therefore the lowest effective dosage, not exceeding 50 mg daily, should be given.

How should acitretin therapy be monitored?

This is the responsibility of the supervising dermatologist; responsibility may be shared with the patient's general practitioner following mutual agreement and locally agreed protocol

- Liver enzymes every 2–4 weeks for the first 2 months of therapy and then every 3 months. If abnormal results are obtained, weekly checks should be instituted and acitretin dose adjusted accordingly. Acitretin should be discontinued if transaminases are elevated to three times their upper normal limit, and patients with bilirubin > 50 μmol L^{-1} or alanine aminotransferase > 200 IU L^{-1} should be referred to gastroenterology. In such cases it is advisable to continue monitoring hepatic function for at least 3 months. However, in those patients where the disease is particularly severe and all else has failed, therapy with acitretin could be continued in consultation with a gastroenterologist and would require a liver biopsy.
- Fasting serum cholesterol and triglycerides every 2–4 weeks for the first 2 months and then every 3 months. In the presence of a good therapeutic response to acitretin but persistently elevated lipid levels, dietary measures should be introduced before considering a lipid-lowering drug. Patients with triglycerides > 5 mmol L^{-1} should be referred to a lipidologist and investigated for other causes of hypertriglyceridaemia (e.g. alcohol, systemic lupus erythematosus, diabetes mellitus, hypothyroidism, renal and hepatic problems, hormonal dysfunction etc.). Hypertriglyceridaemia approaching or over 10 mmol L^{-1} warrants discontinuation of acitretin and urgent referral to a lipidologist, as it is a risk factor for acute pancreatitis.
- Blood sugar levels in diabetic patients on insulin or antiglycaemic agents should also be monitored at similar intervals. These patients should check their capillary glucose more frequently than usual during the first few weeks of treatment.
- Radiological investigation for skeletal changes need not be done routinely as there is a risk from exposure to radiation, the site of ossification is unpredictable and asymptomatic, and abnormal findings are common in normal individuals. However, targeted X-rays are indicated in patients becoming symptomatic.

Audit points

1 Acitretin therapy is not being used in women of childbearing potential where there is a suitable alternative.
2 Where acitretin is used in a woman of childbearing potential contraception is discussed and undertaken for 3 years.
3 Three-monthly laboratory tests are ordered including liver function and lipids, with action if limits are exceeded.

Acknowledgments

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Appendix 1 Level of evidence and strength of recommendation

Level of evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias[a]
2++	High-quality systematic reviews of case–control or cohort studies
	High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal[a]
3	Nonanalytical studies (e.g. case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

Strength of recommendation

Once level of evidence has been derived and evidence tables drawn up, strengths of recommendation can be derived. These are the conclusions of the guideline and it is important that they stand out and stand alone. Often they can be highlighted in a box or a table. The strength of recommendation is determined by the level of evidence although the usefulness of a classification system based solely on this has been questioned because it does not take into consideration the importance of the recommendation in changing practice and it may be that more sophisticated derivations of strength of recommendation will appear in future.

Class	Evidence
A	• At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, **or**
	• A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
	• Evidence drawn from a NICE technology appraisal
B	• A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, **or**
	• Extrapolated evidence from studies rated as 1++ or 1+
C	• A body of evidence including studies rated as 2 +, directly applicable to the target population and demonstrating overall consistency of results, **or**
	• Extrapolated evidence from studies rated as 2++
D	• Evidence level 3 or 4, **or**
	• Extrapolated evidence from studies rated as 2+, **or**
	• Formal consensus
D (GPP)	• A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

RCT, randomized controlled trial.

Supporting Information

Additional supporting information may be found in the online version of this article:

Data S1. Search strategy.

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