

Psoriasis Guideline 2006

Introduction

This guidance for the management of patients with psoriasis is based on a document first produced as a multi-author BAD document in 1996. Since this time the BAD has been developing full evidence based guidelines in many areas that overlap with psoriasis. In addition to azathioprine and biologicals, full guidelines are being prepared for PUVA, acitretin, ciclosporin and methotrexate therapy. In the interim, it was felt sensible to update the existing document so this can still be useful without being out of date or misleading.

The document is principally aimed at dermatologists, but will be helpful to general practitioners and other health professionals, including nurses. It may be necessary or even desirable to depart from the suggested course in the interests of specific patients and special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from the advice in this document should not be necessarily deemed negligent.

Purchasers or commissioners of dermatology services reading this document should pay particular attention to the provision of day care facilities for the outpatient treatment of patients with psoriasis, the provision of inpatient beds for the treatment of patients with severe or intractable psoriasis, and to the provision of the various forms of ultraviolet therapy.

Good quality information for patients helps with decision making, compliance and effective therapy. All important aspects of psoriasis and the relevant treatments are covered in patient information leaflets on this website.

Clinical Features

The diagnosis of psoriasis is clinical, and laboratory investigations are rarely helpful. There are several forms of psoriasis, and an affected individual may move from one type to another. The extent of involvement can range from small areas to almost total coverage. Psoriasis can change from stable plaques to an unstable form, typified by eruptive inflammatory lesions that are easily irritated by topical treatment.

Drugs thought to precipitate or worsen psoriasis include alcohol, lithium, chloroquine and possibly, sometimes beta-adrenoreceptor blocking drugs and ACE inhibitors. Components involved in the assessment of severity should include: the patient's disability, which can be measured by tools such as the Dermatology Life Quality index (DLQI) the need for treatment, together with an objective assessment of the extent and severity of the disease, assessed by PASI score or body surface area affected. Management should take the patient's views into account. It is helpful to record the patient's view of the most upsetting aspect of their psoriasis.

Management strategies can then be directed appropriately within therapeutic limitations based on the risk:benefit ratio.

Quality of Life

Psoriasis may profoundly affect all aspects of patients' social and personal lives as well as their work. The impact of psoriasis on a patient is not directly related to the overall area affected or to other parameters of disease activity such as redness or thickness of plaques, but more to the site distribution and the attitudes of the patient. It is important to be able to measure handicap caused by psoriasis for use in clinical trials, for audit, to aid clinical decision taking. Questionnaire methods of assessment that can be used to measure quality of life include the DLQI (Dermatology Life Quality Index or Children's Dermatology Life Quality Index)

These have been validated and used to assess the effect of systemic therapy and of inpatient therapy. They have been used to compare the impact of psoriasis with that of other skin diseases. A DLQI of 10 or more correlates well with severe disease requiring admission, phototherapy or second line therapy and an improvement in DLQI of 5 or more points is considered a worthwhile criterion for response.

Recommendations for initial treatment and when to refer (joint BAD/PCDS guideline)

- Psoriasis affects 1-2% of the population of the United Kingdom; there is often a positive family history. Most cases are mild
- The degree of psychological and social disability that accompanies psoriasis is commonly underestimated by the medical profession and this can result in suboptimal care

- There is no cure for psoriasis, although there are effective suppressive treatments aimed at inducing a remission or making the amount of psoriasis tolerable to the patient
- For the majority of patients, psoriasis follows a chronic course, interspersed with periods of remission. Relapses are difficult to predict
- The physician should make the patient aware of the possible therapeutic options, including the simplest available therapies and the option that treatment may not be necessary
- The patient's perception of his or her disability will often dictate the need for treatment
- To be able to advise the patient on suitable therapies, the physician needs to know the sites, extent and severity of the psoriasis
- Treatment may depend on the patient's age, sex, occupation, personality, general health, understanding and resources
- Most patients with mild or moderate plaque psoriasis can be treated in primary care using topical therapies
- If the decision is made to refer (see referral) treatment should usually be initiated while awaiting a clinic appointment
- Most patients with uncomplicated psoriasis will only require referral in the instance of treatment failure

Clinical features

- The diagnosis of psoriasis is clinical, and laboratory investigations are unhelpful
- There are several forms of psoriasis, and the type affecting an individual may change over time. The sites and extent of involvement can range from trivial to almost total coverage
- Psoriasis can change from stable plaques to an unstable form, typified by eruptive inflammatory lesions that are easily irritated by topical treatment

- Drugs thought to precipitate or worsen psoriasis include beta-adrenoceptor blocking drugs and NSAIDs. Oral administration of lithium, chloroquine or mepacrine may be associated with severe deterioration of psoriasis. Alcohol may worsen psoriasis and may interfere with treatment in various ways
- Assessment of severity should include the patient's own perception of disability, the need for treatment, and an objective assessment of the extent and severity of the disease
- The total area of involvement is a factor in assessing severity, but is difficult to estimate accurately
- Management should take the patient's views into account. It is helpful to record the patient's views of the most upsetting aspect of his or her psoriasis. Management strategies can then be directed appropriately within therapeutic limitations based on the risk:benefit ratio

Initial presentation

- Basic information about psoriasis and its management should be provided
- To help patients come to terms with what is, for many, a lifelong condition, great efforts should be made to improve communication during consultations and to educate patients
- Patients should have a plan of management, including the therapeutic options for the treatment of their psoriasis at each site involved, and verbal and written information on the probable benefits, and possible side-effects, of each therapy, enabling them to make an informed decision about the treatment
- Ideally, practical demonstrations of the application of treatment should be offered by appropriately trained members of a primary healthcare team
- Points to discuss at initial presentation:
- Explanation of psoriasis, including reassurance that it is neither infectious nor malignant

- Treatment options (including no active treatment)
- The probable benefit the patient can expect from treatment
- Techniques of application of any topical treatment (especially important with dithranol and scalp preparations)
- An introduction to patient support groups may be helpful, e.g. The Psoriasis Association (7 Milton Street, Northampton NN2 7JG Tel - 01604 711129) and the Psoriatic Arthropathy Alliance (PO Box 111, St Albans, Herts AL2 3JQ Tel - 0870 770 3212)

Treatment of chronic plaque psoriasis

- Emollients should be used to soften scaling and reduce any irritation
- For localised plaque psoriasis, e.g. On the elbows or knees, one or more of the following topical preparations can be tried. The sequence of choice will vary according to the extent and pattern of psoriasis, and patient preference:
 - A tar-based cream, or a tar/corticosteroid mixture (most are relatively mild; stronger tar preparations tend to be messy)
 - A moderate potency topical corticosteroid (e.g. 0.05% clobetasone butyrate); stronger agents can be used on palms and soles or on the scalp
 - Use of topical steroids may lead to rebound exacerbation when treatment is discontinued
 - A vitamin D analogue (e.g. Calcipotriol, calcitriol or tacalcitol - the latter two tend to be less irritant and are more suitable for face or flexures, but should still be used with caution)
 - Calcipotriol with betamethasone dipropionate as a combination product (note that long term data regarding relapse rates is not yet established)
- A vitamin A analogue (tazarotene)
- A dithranol preparation, usually used as a short-contact treatment (these are effective but more difficult to use, especially if there are many small lesions)

- For more widespread plaque psoriasis, e.g. On the trunk or the limbs, the same treatments may be appropriate. However, dithranol is often impracticable to apply to multiple small lesions and will irritate flexures. Topical corticosteroids may be inappropriate for use in widespread psoriasis, particularly more potent agents if used on a long-term basis. Application of treatment by appropriately trained nurses may overcome these problems in some cases
- For scalp psoriasis a tar-based shampoo should be tried first; this can be combined with the use of either a 2-5% salicylic acid preparation, a coconut oil/tar/salicylic acid combination ointment, a potent topical corticosteroid preparation (e.g. 0.1% betamethasone valerate), calcipotriol scalp application, or more than one of these
- It is important to use a keratolytic agent (e.g. 5% salicylic acid in emulsifying ointment) first when there is significant scaling, or other treatments will fail. Keratolytic creams should be applied for a few hours or overnight. A different treatment for day- and night-time is a useful approach
- In palm and sole psoriasis, as for the scalp, both hyperkeratosis and inflammation are usually present and may require separate treatments. Hyperkeratosis usually needs to be treated with a keratolytic agent. Topical steroids (usually potent, due to the thick skin at this site), tars and vitamin D analogues may all be useful
- In general, milder agents are used for flexures. These include low potency topical steroids, mild tar preparations, and tacalcitol or calcitriol (not calcipotriol, this is usually irritant in flexures)
- In facial psoriasis, use mild agents: emollients, mild corticosteroids, calcitriol, tacalcitol, mild tars

Referral

- Those patients with extensive disease who need secondary care treatments such as systemic treatment or phototherapy will normally be under the supervision of a consultant

dermatologist because of the potential adverse effects of these approaches

- The dermatologist will also be involved in the care of difficult cases where the site or unresponsiveness of the rash are important factors

Indications for consultant referral:

- Diagnostic uncertainty
- Request for further counselling and/or education including demonstration of topical treatment
- Failure of appropriately used topical treatment for a reasonable time (e.g. 2-3 months)
- Extensive disease, if unresponsive to initial therapy or difficult to self-manage
- Need for increasing amounts or potencies of topical corticosteroids
- Involvement of sites which are difficult to treat, e.g. Face, palms and soles, genitalia, if unresponsive to initial therapy
- Need for systemic therapy, phototherapy (e.g. guttate psoriasis), day treatment or inpatient admission
- Generalised erythrodermic or generalised pustular psoriasis (emergency referral is indicated); acute unstable psoriasis (urgent referral may be justified)
- Adverse reactions to topical treatment
- Occupational disability or excessive time off work or school

Content of the referral letter:

- The reason for referral and what is hoped to be gained from the consultation
- The consultant should try to address these issues in reply
- The patient's present therapy, if any, its duration, and quantity being used

- Information on previous therapy, including responses or side-effects
- A treatment could be mistakenly recorded as ineffective when the real problem was under-treatment or incorrect use of the prescribed treatment, or discontinued as unsuitable when transient side-effects could have been overcome had more advice been given
- Any relevant background information, including the patient's general health and current medication
- The patient's home circumstances; important because the patient's ability to apply topical therapies at affected sites may be compromised, affecting treatment choice

Topical therapy

Topical Coal Tar

Coal tar has been used to treat psoriasis over many years. Although often considered to be safe, there have been doubts about its safety since the 1940's, and recent evidence has provided further evidence on this. There are several commercially available creams, which contain between 0.4% and 2% crude coal tar, and also shampoos, which have a coal tar content of up to 2.5%. Crude extracts of coal tar can be made up in white or yellow soft paraffin, or emulsifying ointment. Coal tar solution is already diluted, so the true concentration of tar in commercial tar products is lower than stated and not equivalent to crude coal tar.

Efficacy

Coal tar is an effective treatment for inducing remission in psoriasis. Coal tar preparations of between 1 and 5% in white or yellow soft paraffin are as effective as higher concentrations. The use of higher concentrations, which has been traditionally advocated, has no evidence-based foundation and is best avoided, especially as it restricts outpatient use.

Safety, side-effects and patient acceptability

Coal tar preparations smell. The crude extract preparations smell more and are messier to use. Recently there has been renewal of concern about the potential carcinogenicity of coal tar products. Occupational exposure to coal tar is associated with an increased risk of skin cancer, and some studies have shown that skin cancers

are more common in patients with psoriasis, although not all studies were controlled for the confounding effects of smoking and alcohol consumption, and many squamous cell carcinomas are accounted for by the effects of photochemotherapy, which may mask other effects. Experimental studies have shown that the use of coal tar shampoos results in the absorption of appreciable amounts of polycyclic aromatic hydrocarbons (PAH), substances identified as being carcinogenic. In view of this, the Dutch delegation to the European Commission has suggested limiting the concentration of benzo[a]pyrene (one of the carcinogens known to be in coal tar) in commercially available coal tar products. In Germany, cosmetic manufacturers have voluntarily agreed to ban coal tar from their shampoos.

Despite the above, there is at present, no firm epidemiological evidence that topical tar products cause cutaneous or internal cancer. The extent of percutaneous absorption of tar derivatives in tar-treated patients with psoriasis is currently unknown. It is considered reasonable, therefore, for topical tar containing products remain available.

Synergy with other treatments

Tar treatments act synergistically with ultraviolet B radiation in the traditional Goeckerman regimen. This can be a very effective method of clearing mild psoriasis. In addition, there are reports suggesting that tar and topical steroids have a synergistic effect, and some dermatologists adopt a regimen of a moderately potent topical steroid by day, with tar by night, for ease of patient use. A modified Goeckerman regime using narrow band UVB as the adjunct achieved PASI 75 (75% improvement or more in PASI score) in 95% of cases.

References

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Van Schooten FJ, Moonen EJC, Rhijnsburger E, et al. Dermal uptake of polycyclic aromatic hydrocarbons after hairwash with coal-tar shampoo. *Lancet* 1995; 344: 1505-6

Zackheim HS. Should coal tar products carry cancer warnings? *Cutis*. 2004 May;73(5):333-4.

Lee E, Koo J. Modern modified 'ultra' Goeckerman therapy: a PASI assessment of a very effective therapy for psoriasis resistant to both

prebiologic and biologic therapies. J Dermatolog Treat. 2005 Apr;16(2):102-7.

Topical Dithranol

Dithranol has been used for over 50 years in the treatment of stable plaque psoriasis and remains an effective, inexpensive and extensively used topical remedy, without long term local, systemic or teratogenic effects.

Efficacy

Treatment is designed to limit dithranol application to the affected skin by applying dithranol (0.1-2%) in a non-smudging zinc oxide (Lassar's) paste. This is applied to each plaque by a trained nurse or tutored patient and, after covering with powder and Stockinette to reduce smearing, left on for up to 24 hours. Treatment is frequently combined with UVB phototherapy and a tar bath (the Ingram regimen). Patients with plaque psoriasis respond after approximately 20 days of treatment, and relapse at a rate of 10% per month.

Because of the difficulty in its application, this type of dithranol treatment is normally carried out under hospital supervision. Cream or ointment based preparations may smudge onto and, hence, burn, surrounding unaffected skin when used as overnight applications. Application of high concentrations of dithranol (1-10%) for 15-30 minutes daily (short contact therapy), followed by wash-off, allows sufficient dithranol to remain fixed to the plaques for a clinical effect to be obtained without the need for special dressings, as there is less risk of smudging of dithranol onto peri-lesional skin. Skin irritancy may still occur when dithranol is smeared on normal skin during wash-off.

Patients require a careful explanation or, ideally, a demonstration of the technique. Preparations such as dithrocream are available in multiple concentrations. Normally treatment is started at a lower concentration with each course of treatment and gradually increased within the patient's tolerance, reducing the strength if there is burning and increasing it where possible. Response can be gauged by palpating the plaque. Once lesions are palpably flat dithranol should be discontinued.

Safety, side-effects and patient acceptability

The immediate unwanted effects of skin staining and irritancy, however, limit its use. Brown dithranol staining of treated skin (temporary) and fabrics or bathroom fittings (permanent), is common to all dithranol treatment techniques, and reduces patient acceptability. Skin irritancy is also a problem. Involved psoriatic skin is more resistant to irritancy than the clinically normal peri-lesional skin

Synergy with other treatments

The addition of UVB phototherapy prolongs remission. Comparison of the Ingram and short contact dithranol therapies shows a similar outcome. Dithranol must only be used under expert guidance on the face and flexures, because of the risk of skin or eye irritancy.

Topical Vitamin D Analogues

Three vitamin D analogues are available in the UK for topical treatment of psoriasis, namely calcipotriol, calcitriol and tacalcitol.

Calcipotriol

Calcipotriol is available in ointment and cream formulations containing calcipotriol at the concentration of 50 microg/g, and as a scalp lotion (50 microg/ml). Treatment may be used once or twice daily. Improvement usually becomes apparent within 2 weeks, and continues for at least 8 weeks, at which point some patients are clear but the majority reach a plateau. In the latter case, the improvement can often be maintained by continuing treatment. Calcipotriol is safe, provided that the manufacturer's recommendations are followed and the maximum dose 100g/week for adults, 75g for children over 12 and 50g for children of 6-12 years is not exceeded. Use in children under 6 is not recommended. Calcipotriol is more convenient to use than tar or dithranol and does not produce the side effects of topical corticosteroids. However, self limiting, irritant reactions are common. Calcipotriol has become one of the first-line treatments for psoriasis vulgaris.

Efficacy

Calcipotriol is an effective treatment for mild to moderate chronic plaque psoriasis, more so than calcitriol, tacalcitol, coal tar, and short contact dithranol. Only potent topical corticosteroids seem to have comparable efficacy at eight weeks. Although calcipotriol causes more skin irritation than topical corticosteroids this has to be

balanced against the potential long term effects of corticosteroids. Skin irritation rarely led to withdrawal of calcipotriol treatment.

Use in pregnancy: Although calcipotriol is not believed to be teratogenic, there is little experience of its use in pregnancy.

Safety and side effects

Calcipotriol is irritant and may give rise to redness, soreness or pruritus in around 20% of patients during 6 weeks of treatment. Such reactions are particularly common when the face is inadvertently contaminated with medication. This is self-limiting but occasionally necessitates a break in treatment. This irritancy largely precludes the use of calcipotriol on the face. Flexures are also vulnerable. The maximum recommended rate of usage is 100g of ointment weekly. This should not be exceeded, as there is a risk of vitamin D intoxication.

When doses below 100g weekly have been used, no evidence of any effect has been observed. However, at 100g weekly a small increase in urine calcium excretion is detectable. When the dose rate is increased to 200g or 300g weekly, both urine and serum calcium levels rise, and serum parathyroid hormone is depressed. There are now a number of reports of individual patients in whom hypercalcaemia has developed when the maximum recommended dose rate has been exceeded. Absorption of the vitamin D analogue may be higher in erythrodermic psoriasis, and hypercalcaemia has been reported in such a case when 200g of ointment were applied in 7 days. In another erythrodermic patient, hypercalcaemia developed when using 100g of ointment weekly, and recurred when the treatment was reintroduced at a lower dose rate. There have been four reports of probable sensitisation to calcipotriol. Experience has not led to concern over the risk of psoriasis rebounding after topical calcipotriol, in a manner similar to that said to occur with topical corticosteroids.

Patient acceptability

Calcipotriol is an improvement on previously existing topical treatments for psoriasis, except for those patients who use emollients alone. Compared to dithranol, it is less irritant, less messy and more convenient. Patients' opinions regarding the acceptability of these treatments have been directly compared in a large trial: calcipotriol

was considered more acceptable. It is less messy than tar, and is free from the odour of tar, which some patients dislike. Calcipotriol is free from the side effects of topical corticosteroids, which are a source of concern to patients. Calcipotriol is often irritant. Although this is a disadvantage, it is only occasionally necessary for treatment to be discontinued as a result.

Synergy with other treatments

Published data suggest that there is a useful additive effect when calcipotriol is used in conjunction with PUVA, cyclosporin, and UVB. It would appear possible that the use of calcipotriol may allow a useful dose sparing effect with UVB phototherapy or PUVA, and systemic treatments, and thus reduce their toxicity, but more research is required to address this question.

References

Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: a systematic review. *Br J Dermatol.* 2002 Mar;146(3):351-64.

Calcitriol

This ointment contains vitamin D in the form of 1:25 dihydroxy-cholecalciferol, at the concentration of 3 microg/g. Advantages of calcitriol are that it is less irritant than calcipotriol and may, therefore, be suitable for use on the face and flexures. Duration of remission is greater than with potent topical steroids. The rate of application should not exceed 30g ointment per day and it should not be applied to more than 35% of the body surface daily. More published data are currently needed, before clear guidelines can be issued to establish the precise role of this product. It is a clean non-smelly preparation which is well tolerated and more effective than short contact dithranol therapy.

Use in pregnancy and children

Calcitriol has not been licensed in children and not adequately assessed in pregnancy. There is some evidence in animals of

developmental toxicity at doses, which caused maternal toxicity, and calcium levels should be monitored in situations where it has been used in restricted amounts out of necessity. It also passes into breast milk and should be avoided in breastfeeding.

Tacalcitol

Tacalcitol 4 microg/g is also less irritant but less effective than calcipotriol. It is suitable for use on the face and flexures and the amount applied should not exceed 10g/day. It has not been licensed for use in children and although no toxicity has been found there is insufficient data to support its use in pregnancy and lactation.

Calcipotriol/betamethasone dipropionate

A novel ointment comprising betamethasone 0.05% (as dipropionate), calcipotriol 50 micrograms/g has greater efficacy than either constituent used alone. However, the cost of treatment is also greater and the restrictions that apply to potent topical steroids in psoriasis (see below) apply.

It is normally used in the initial treatment of stable plaque psoriasis where calcipotriol has failed. Patients should be instructed to apply once daily to a maximum of 30% of body surface for a maximum of 4 consecutive weeks; max 15 g daily, max 100 g weekly. After this period repeated treatment with Dovobet can be initiated under medical supervision. A frequent compromise is to use the combined product for 4 weeks alternating with 4 week periods of Calcipotriol. Over the 52 weeks this alternating combination optimised response with the least side effects. It is not recommended for children and adolescents under 18 years and is unsuitable for use on the face or flexures.

Potent topical corticosteroids should be avoided or given only under specialist supervision in psoriasis because, although they may suppress the psoriasis in the short term, relapse or vigorous rebound occurs on withdrawal (sometimes precipitating severe pustular psoriasis). Topical use of potent corticosteroids on widespread psoriasis can lead to systemic as well as to local side-effects

Tazarotene

Tazarotene (0.05% and 0.1%) gel is a topical retinoid which is effective in psoriasis. It is clean and odourless and should be applied once daily for 12 weeks. Irritation is common but it is minimised by adjusting the strength of the treatment and by applying tazarotene sparingly to the plaques, avoiding normal skin. It is suitable for the treatment of moderate plaque psoriasis affecting up to 10% of skin area. Patients should be instructed to wash their hands immediately after use, avoid contact with eyes, face, skin folds, hair-covered areas of the scalp, and eczematous areas. They should also avoid excessive exposure to UV light (including sunlight, solariums, PUVA or UVB treatment) and should avoid applying emollients or cosmetics to the treated area within 1 hour of application

Use in pregnancy and children

As a retinoid this preparation is potentially teratogenic and should strictly be avoided in pregnancy. Women of child-bearing age must ensure adequate contraceptive protection. It is not recommended for use in breastfeeding mothers or children/adolescents under the age of 18.

Side-effects:

Side effects include local irritation (more common with higher concentration and may require discontinuation), pruritus, burning, erythema, desquamation, non-specific rash, contact dermatitis, and worsening of psoriasis; rarely stinging and inflamed, dry or painful skin

Topical Corticosteroids

Topical Corticosteroids are effective, cosmetically acceptable and safe if used carefully under supervision.

Efficacy

A wide selection of products is available ranging from very mild (e.g. 1 per cent hydrocortisone) to highly potent (e.g. 0.05 per cent clobetasol propionate) enabling accurate titration of the potency of the preparation prescribed against the patient's needs. The potency of the cream or ointment used depends not only on the inherent activity of the steroid molecule itself and its concentration, but also on the excipient in the vehicle used in the formulation. Topical corticosteroids are best used on limited areas of psoriasis. More

resistant areas such as the hands, feet and scalp can initially be treated by potent corticosteroids from the onset. There is no evidence that twice daily application of topical steroids is more effective than once daily application. The strength of the steroid should be adjusted commensurate with clinical improvement. In especially resistant psoriasis of the limbs, hands or feet, occlusive treatment in which the treatment area is covered by a thin polythene film will greatly enhance effectiveness (and also local and systemic toxicity). This measure should only be continued for a few days at a time. Flexural areas are usually self occluded and therefore require only mild potency topical steroid treatment, as does the face and neck.

Safety, side-effects and tolerance

Corticosteroid resistance (tolerance) may develop and the use of corticosteroids may be accompanied by local side effects especially if occlusive therapy has been used. These include thinning of the skin and telangiectasia (usually reversible) and irreversible steroid striae. Other side effects include rapid relapse time and transformation to unstable or pustular psoriasis. In extreme cases systemic toxicity including pituitary adrenal suppression and the clinical features of Cushing's syndrome may be caused by extensive percutaneous absorption. These risks are related not only to the potency of the preparation used but also to the total daily amount applied. If appropriate guidelines are followed (below) the use of a British National Formulary mild steroid on the face and flexural areas, and a moderate or, in exceptional circumstances and for a short period a high potency corticosteroid elsewhere is acceptable.

Rarely glaucoma may occur from the use of topical steroids on the eyelids and periorbital area. Systemic toxicity is also more likely to occur in infants and small children because of the large surface area relative to mass. Tolerance may occur in response to continued use of any topical steroid and is related to duration of use rather than potency. Its mechanism is unknown. Use of alternative non-steroid topical treatment usually results in recovery of responsiveness to the corticosteroid. Contact allergy is occasionally a complication of topical corticosteroid treatment and can be confirmed by appropriate patch testing. Newer steroids including mometasone, prednicarbate and fluticasone propionate are more rapidly inactivated or metabolised following percutaneous absorption although retaining local efficacy and local potential for adverse effects. No unsupervised repeat prescriptions should be made: patients should be reviewed every 3 months

- No more than 100 g of a moderately potent or higher potency preparation should be applied per month
- Attempts should be made to rotate topical corticosteroids with alternative non-corticosteroid preparations
- Use of very potent or potent preparations should be under dermatological supervision. The fingertip unit is a measure which helps patients to know how much ointment or cream to apply.
- No topical corticosteroid should be used regularly for more than four weeks without critical review.
- Potent corticosteroids should not be used regularly for more than 7 days.

Synergy with other treatments

A topical corticosteroid can be used as a monotherapy or in conjunction with other topical agents including tar or dithranol. Some patients who fail to respond to one topical agent may respond to another and it is worthwhile rotating different classes of topical agents before abandoning topical treatment altogether.

Specific Sites

Chronic Plaque Psoriasis

Depending on patients' wishes, appropriate management includes the option of no active treatment. If active treatment is required, most patients can be adequately managed with topical agents of proven efficacy including the use of a simple emollient, dithranol, corticosteroids and vitamin D analogues. Each patient must be individually assessed. Large individual psoriatic plaques can be treated with dithranol, tar or vitamin D analogues. Smaller and more numerous lesions are more difficult to treat with dithranol, but vitamin D analogues, mild tar preparations and corticosteroid are still appropriate. The effect of topical treatments can usually be enhanced by UVB phototherapy.

Care is needed when a patient's psoriasis is in an inflammatory, eruptive or unstable phase. In these circumstances, the skin may show general, non-specific irritancy to topical agents, and treatment

should be confined to emollients or low concentrations of tar, corticosteroids or dithranol.

Guttate Psoriasis

In most cases, guttate (exanthematous papulosquamous) psoriasis is a self-limiting condition. Many patients who have one attack of guttate psoriasis have no further relapses. The general principles for treatment outlined above are applicable to guttate psoriasis. Erupting guttate psoriasis is commonly less tolerant of topical therapy, and therefore calcipotriol, mild or moderately potent corticosteroids, or low concentrations of tar and dithranol should be used. UVB phototherapy may be helpful. A proportion of patients with acute guttate psoriasis have evidence of recent streptococcal infection, which can be confirmed by culture examination of a throat swab and by determination of the serum antistreptolysin O titre. Evidence does not support a therapeutic benefit from antibiotic therapy. However, repeated attacks of guttate psoriasis after well documented episodes of tonsillitis represent an indication for tonsillectomy.

Localised Pustular Psoriasis of Palms and Soles

Pustular psoriasis of the palms and soles is a relatively rare form of chronic psoriasis typified by multiple sterile pustules. Treatment is unsatisfactory but calcipotriol or a potent topical corticosteroid may help. Topical coal tar and dithranol may also be of some benefit and some success can be achieved with the systemic agent acitretin or with photochemotherapy (8-methoxypsoralen-UVA phototherapy; PUVA). In disabling palmoplantar psoriasis systemic therapy may be required with acitretin or methotrexate.

Generalised Pustular and Erythrodermic psoriasis

For the small group of patients with these forms of psoriasis, initial management usually consists of admission to hospital and the use of systemic agents.

Psoriasis of the Scalp

This form of plaque psoriasis can be difficult to manage especially in a domiciliary setting. Thick scale should be softened, by olive, coconut or arachis oil, ideally applied under occlusion (e.g. using a plastic shower cap or cling film), then removed using a detergent shampoo. This can be followed by applications of a coal tar, dithranol, or a topical steroid or vitamin D analogue preparation.

Topical salicylic acid preparations, e.g. 2% salicylic acid in a cream base such as Unguentum M, or coconut oil ointment (e.g. Cocus scalp ointment), can be used to remove thick scale from the scalp.

Phototherapy

Both therapies require good metering and equipment monitoring by trained staff. All patients should be aware of the adverse effects and chronic risks, and a detailed record of an individual's treatment should be kept.

UVB Phototherapy

Broad band ultraviolet radiation in the waveband 290-320 nm (UVB), or narrow band UVB 311nm are an effective treatment of guttate or plaque psoriasis resistant to topical therapy. It is initiated by experienced dermatologists and is administered under supervision of trained dermatology nursing staff or physiotherapists. Patient compliance is usually good, with the treatment viewed as an escape from the problems of topical agents. Restrictions in use for individual patients often relate to time off work and travel costs.

Within the UK, a range of equipment is in use. The older broad-band UVB fluorescent sources are considered less effective, in time to clear and length of remission period. Narrow-band (311nm) phototherapy emits light close to the peak therapeutic wavelengths for psoriasis and has a greater efficacy than broad-band fluorescent tubes. Further guidelines on dosimetry and monitoring are available on this site (BAD guidelines)

Safety, side-effects and patient acceptability

Current human use suggests that TL-01 has a similar long-term risk to the older broad-band tubes and a reduced risk when compared to PUVA

Those patients who have a history of previous skin malignancy, systemic lupus erythematosus or xeroderma pigmentosum, should be excluded from treatment. UVB phototherapy has advantages over PUVA in that it can be used in children, during pregnancy, and does not require photoprotective spectacle use post-treatment. The principal unwanted effects of UVB phototherapy are acute skin burn, which can be avoided by careful dosimetry, and, when used over a long period, a presumed dose-related increase in the risk of developing cutaneous malignancy.

Efficacy

Although UVB phototherapy has been extensively studied, dosage regimens vary, and it seems that different skin type populations require different treatment approaches. The starting dose of UVB can be judged by estimation of the minimal erythema dose (MED). This approach is not essential, and a low dose fixed increment regimen is an acceptable alternative. A suggested approach is to start at 70% of the MED value. Subsequent doses can be increased by 40% of the immediately preceding dose, if there is no erythema, and 20% if there is a slight erythema, or held at the same exposure, if there is a marked response to the previous treatment. With such a regimen, treatments are generally given no more frequently than every two days. It is usual for a course of UVB phototherapy to take between 10 and 30 treatments to achieve clearance

Synergy with other treatments

Combination with other anti-psoriasis treatments such as tars, topical calcipotriol, and oral retinoids have been shown to be effective, increasing the rate of clearance with reduced total UVB exposure to clearance. However, most patients enjoy the freedom from topical therapies and their accompanying adverse effects, so adjunctive treatment is often reserved for resistant cases.

Photochemotherapy (PUVA)

Administration of oral or topical psoralens, followed by irradiation with long wave ultraviolet (320 to 400nm) (UVA), is an established, effective, widely used form of treatment (Psoralens + UVA = PUVA), although it is unlicensed in the UK. While it does have acute adverse effects (i.e. skin burning, nausea and pain) and chronic consequences (i.e. skin ageing, pigmentation and carcinogenicity), it continues to be used for more difficult to clear psoriasis resistant to topical preparations and UVB. Examples of different regimens for the administration of PUVA are listed in the British Photodermatology Group Guidelines for PUVA. Other detailed information sources are available.

Efficacy

Two main PUVA regimens are used. The first involves the use of the minimal phototoxic dose (MPD) to determine the first treatment dose of a course. Such an approach would be similar to that used for UVB phototherapy with, perhaps, 70% of the MPD, followed by successive

doses increased by 40% increments, if there is no erythema, or 20% if the erythema response was slight. As the phototoxic effect is maximal at 48 to 72 hours, treatment is usually given twice weekly. Another approach has a fixed starting dose, which will vary with skin type, followed by fixed or percentage increments as above. No adequate studies have been published to state clearly which approach is best for a particular patient populations. It is common practice for 8-methoxypsoralen (crystalline 8-MOP) to be taken orally 2 hours prior to UVA irradiation. To achieve consistent and optimal absorption of psoralens throughout a course of PUVA, the drug should be taken with a light meal.

Safety, side-effects and patient acceptability

As there is a theoretical risk of cataract formation, patients are advised to wear eye protection for 24 hours from the time of psoralen ingestion. Further advice on eye protection can be found elsewhere on this site (BAD guidelines). If nausea occurs with 8-MOP, 5-methoxypsoralen or bath PUVA using 8-MOP or trimethoxypsoralen (TMP), can be considered. Some centres use the bath approach as the routine, preferring the confidence of knowing the drug to be at the target site, coupled with the possibility that TMP and PUVA may be less carcinogenic than oral forms.

As the risk of developing cutaneous malignancy is related to the number of treatments or the cumulative dose of UVA, PUVA-sparing measures, or alternative treatments, can be used to restrict the total amount of UVA administered. In a follow-up report on the large North American cohort group, it is suggested that patients may be at long term risk of developing squamous cell carcinoma after as little as 120 treatments of PUVA. Those who have had more than 300 treatments have 83 times the risk of developing squamous cell carcinomas which can be multiple and metastasising. Some patients are particularly susceptible, due to other risk factors (e.g. exposure to concomitant methotrexate, ionising radiation or arsenic). This suggests that long-term follow up of high dose PUVA patients is important. Although maintenance PUVA therapy is not recommended, and has been associated with the development of squamous cell carcinoma, informed patients may choose to continue with this approach if no safer alternative treatment exists. Some evidence suggests that Melanoma incidence may increased many years after PUVA therapy, although the North American study was not consistent with the experience in Northern Europe.

Synergy with other treatments

As with UVB, adjunctive therapy using vitamin D analogue preparations, and retinoids, have been shown to be effective and are worth considering if PUVA monotherapy is inadequate.

Operation of phototherapy services

- A senior clinician, usually a consultant, with adequate training and a continuing interest in phototherapy and/or photochemotherapy should supervise the service
- An individual patient's course of therapy should be supervised by an adequately trained person (e.g. a doctor, nurse or physiotherapist)
- All phototherapy equipment should be adequately maintained and regularly calibrated by adequately trained personnel
- Accurate records of the dosage and number of treatments, for each patient, must be maintained
- Neither UVB nor PUVA should be used as permanent maintenance therapy unless alternative topical therapies have proved ineffective

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Systemic therapies for psoriasis

For an excellent evidence based review of systemic therapy see Griffiths CE, Clark CM, Chalmers RJ, Li Wan Po A, Williams HC. A systematic review of treatments for severe psoriasis. Health Technol Assess. 2000;4(40):1-125

Indications for Systemic Therapy

- Failure of adequate trial of topical therapy
- Repeated hospital admissions for topical therapy
- Extensive chronic plaque psoriasis in the elderly or infirm
- Generalised pustular or erythrodermic psoriasis
- Severe psoriatic arthropathy
- Patients considered for systemic therapy will usually conform to the rule of tens whereby the body surface area affected is greater than 10%, or the PASI score is greater than 10 or the DLQI is greater than 10.

Methotrexate

Methotrexate is an effective antipsoriatic agent. It is especially useful in acute, generalised, pustular psoriasis, psoriatic erythroderma, psoriatic arthritis, and for extensive chronic plaque psoriasis in patients who are inadequately controlled by topical therapy alone. In comparison with other systemic therapies for psoriasis, it is inexpensive and of comparable efficacy. It can be used either as a short term option, to gain control of unstable psoriasis such as pustular psoriasis or erythroderma before returning to the other

modes of treatment, or, more often, as long term maintenance treatment. The most important potential side effect is acute marrow suppression, which is the cause of most of the rare deaths attributable to methotrexate therapy of psoriasis. Long term treatment carries with it a risk of hepatic fibrosis and cirrhosis, which is related to the dosage regimen employed, and is increased by exposure to other hepatic toxins, in particular alcohol. The correlation between the cumulative lifetime dose of methotrexate and the risk of development of hepatic fibrosis or cirrhosis is not clear-cut.

Safety, side-effects and patient acceptability

Haematological or renal abnormality: Methotrexate should be avoided in patients with significant haematological abnormalities including severe anaemia, leucopenia or thrombocytopenia. Methotrexate should also be avoided, in all but exceptional circumstances, in patients with significant renal impairment. Because methotrexate is eliminated largely via the kidneys, toxic levels may build up rapidly in patients with renal impairment, and even low doses of the drug may then produce acute myelosuppression. This is particularly liable to occur in the elderly when concomitant drug administration or illness, such as fever or diarrhoea, may result in the sudden deterioration of renal function. Elderly patients especially, should be warned to omit methotrexate doses whenever they are at risk of acute dehydration (e.g. from acute fever, vomiting or diarrhoea).

Drug Interactions: Certain drugs may increase the toxicity of methotrexate by increased antifolate effect (e.g. sulphonamides, trimethoprim and phenytoin), or by decreasing renal elimination (e.g. aspirin, NSAIDs, probenecid and cyclosporin). As life-threatening myelosuppression may result from interactions between methotrexate, and such drugs, great care must be taken to ensure that all medical attendants are made aware when a patient is receiving methotrexate and patients should be advised to check with their pharmacist on the safety of any new drug prescription they receive.

Liver disease and alcohol: Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. Any patient suspected of alcohol abuse is usually unsuitable for methotrexate, although many dermatologists allow patients receiving methotrexate to continue taking small amounts of alcohol (e.g. 4-6 units weekly).

Fertility: Because methotrexate is both abortifacient and teratogenic it is strictly contraindicated in pregnancy. Adequate contraceptive measures must be taken by women of child-bearing potential during methotrexate therapy, and for at least three months after stopping the drug. Although methotrexate is not mutagenic, and normal children have been born when the father was taking methotrexate at the time of conception the drug may affect spermatogenesis. Men should therefore be advised to avoid fathering children during therapy and for three months after. Discontinue methotrexate and refer immediately if a patient or partner discovers they are pregnant while taking methotrexate

Other precautions: Other important contraindications to the use of methotrexate in psoriasis include active peptic ulceration, active infectious disease, such as tuberculosis or immunodeficiency states, and patient unreliability.

Prescribing methotrexate

Initiation of therapy: The risks and benefits of therapy should be clearly explained to the patient, both verbally and in writing. In addition to the patient information leaflet on this web-site the BAD have produced a hand held patient information leaflet that complies with the National Patient Safety Agency directives for safe use of this of therapy and a hand held patient record to facilitate patient monitoring. These will be available in early 2006. A clear record of the history (including previous therapy), and the extent of psoriasis, should be made. Adequate contraceptive measures must be commenced where appropriate. A full blood count and tests of renal and hepatic function (see below) should be performed. If there are no contradictions, then therapy may be commenced. The dose of methotrexate must be individually assessed for each patient. Most serious problems and the rare deaths associated with methotrexate usage in psoriasis arise because of an absolute or relative overdose.

Methotrexate is usually given orally but may be administered by the intramuscular or intravenous route. Recently the subcutaneous route has become more practical with the advent of the biological therapies. Details of the subcutaneous route to maximise bio-availability and improve tolerance and safety are to be found on <http://www.rcn.org.uk/publications/pdf/administering-methotrexate.pdf> It should be given as a single weekly dose. For oral dosing the BAD recommend all patients be prescribed the 2.5mg tablets to avoid

confusion and overdosing on the 10mg tablet formulation. Unambiguous instructions, including which day of the week the tablets are to be taken, should be given to the patient and specified on the prescription. The rationale proposed for giving methotrexate in three divided doses once weekly is obsolete as this schedule is more open to error and may be associated with a greater risk of hepatic fibrosis.

A small test dose, usually 5mg, should be given in order to detect those patients who may be unduly sensitive to the drug. If the full blood count is stable, at seven days, then methotrexate may be continued. Subsequent doses may be gradually increased, usually by 2.5-5 mg steps, according to clinical response and any accompanying toxicity. The aim of therapy should not be to induce complete clearance of psoriasis but to achieve sufficient control that it may be more readily managed with topical therapy. Most patients are adequately controlled on doses of 7.5-15mg weekly and few patients require more than 20mg. The maximum weekly dose should not exceed 30mg. Lower doses are required in the elderly and those with renal impairment.

Monitoring therapy: Initially, patients should be assessed weekly by examination and laboratory measurement of the full blood count, plasma urea, electrolytes and creatinine, and liver enzyme tests. The interval between visits may be gradually increased until therapy has been stabilised, after which continuing assessments should be performed every two to three months. The exact time intervals will vary according to circumstance. Mechanisms should be in place to ensure that further supplies of the drug are dispensed only if appropriate monitoring has been carried out, and that blood test results are reviewed promptly after each visit so that any necessary action, such as dosage reduction, can be taken without delay. In any individual the dose of methotrexate required to maintain adequate control of psoriasis will vary from time to time, and should be adjusted accordingly.

Although liver biopsy is the gold standard measure for hepatic fibrosis due to methotrexate it carries significant risks and the need for this intervention can be considerably reduced by monitoring the serological markers of fibrosis, particularly the aminoterminal peptide of type III procollagen (PIIINP). Patients whose PIIINP levels are consistently normal are very unlikely to have significant liver damage, and liver biopsies may be restricted to the small minority in whom PIIINP levels are repeatedly elevated. PIIINP assay should be performed three monthly and liver biopsy should then be considered

for patients in whom it is persistently abnormal (i.e. greater than 4.2ng/ml for the Orion assay).

Where possible, serum should be collected for PIIINP measurement prior to starting methotrexate. It should subsequently be measured every 2-3 months during continued treatment.

Indications for Considering Liver Biopsy:

- Elevation of pre treatment PIIINP above 8.0 mcg/l
- Elevation of PIIINP above normal range (1.7-4.2mcg/l) in at least three samples over a 12 month period.
- Elevation of PIIINP above 8.0mcg/l in two consecutive samples.

Indications for considering withdrawal of methotrexate:

- Elevation of PIIINP above 10 mcg/l in at least three samples in one 12 month period.

The decision whether to ***perform liver biopsy, withdraw or continue*** treatment ***despite raised PIIINP levels*** must also take into account ***other factors*** such as ***disease severity, patient age and the ease with which alternative therapies may be used in place of methotrexate.***

As alcohol abuse greatly increases the risks of liver damage in patients receiving methotrexate, they should be reminded regularly of the need to restrict or avoid alcohol intake. Liver damage cannot be reliably detected by standard liver enzyme tests. The risk of serious liver damage in carefully monitored patients receiving once weekly low dose methotrexate is small and the cost and morbidity of repeated liver biopsy may be difficult to justify when compared with the low yield of significant liver pathology. It is, thus, reasonable to recommend that liver biopsy need no longer be performed routinely. If there are concerns about pre-existing liver damage, it may be appropriate to obtain a liver biopsy as a baseline soon after successful methotrexate therapy has been established. The best practice for liver biopsy is for this to be done, by radiologists, under ultrasound control.

Management of problems: Nausea is the commonest side effect reported by patients and may affect up to a quarter of all patients treated. It usually appears within 12 hours of methotrexate ingestion and may last up to three days. It is usually mild, but in some patients, it is sufficiently severe enough to necessitate withdrawal of therapy. No measures are guaranteed to relieve symptoms. The subcutaneous administration has helped reduce problems with gastrointestinal intolerance.

Folic acid, supplementation has been found to be helpful in preventing folate deficiency, reducing myelotoxicity and improving tolerance of methotrexate. It is broadly recognised that folate supplementation should be initiated with methotrexate therapy although practice varies regarding the dose. Commonly it is taken on the 6 days of the week when methotrexate is not taken. The minimum dosage recommended is 5mg taken once weekly.

Although liver enzyme tests are an unreliable indicator of liver fibrosis, an acute rise in liver enzymes may indicate hepatic inflammation. If aspartate or alanine aminotransferase levels rise to greater than three times the upper limit of normal methotrexate would normally be discontinued.

The decision to discontinue methotrexate depends not only on PIIINP and/or the results of liver biopsy, but also on the ease with which an individual patient's psoriasis may be managed by other means. Severe fibrosis and cirrhosis are considered contraindications to further methotrexate therapy. Nevertheless some dermatologists have continued treatment in patients with documented cirrhosis without encountering significant deterioration of liver disease. In patients with hepatic inflammation or mild to moderate fibrosis without cirrhosis, continuation of methotrexate therapy is probably still safe, as long as alcohol is strictly avoided and patients are closely monitored. If PIIINP remains elevated, then a further liver biopsy should be considered, after twelve months to two years of continued therapy.

A rise in the mean corpuscular volume (MCV) is common in patients receiving long term methotrexate, and usually indicates relative folate deficiency. If the MCV rises above the upper limit of normal, folate deficiency is likely and supplementation may be inadequate. If this occurs, it is important to exclude other causes of macrocytosis, in particular vitamin B12 deficiency. If the MCV rises above 106 fl, despite folate replacement, then further methotrexate therapy is probably contraindicated. It is important to note that folate therapy does not reduce the therapeutic effect of methotrexate.

Managing overdose

Absolute or relative overdose of methotrexate can result in acute toxicity, manifested clinically by myelosuppression, mucosal ulceration and, rarely, cutaneous necrolysis. The metabolic effects of methotrexate can be bypassed by the administration of folinic acid, which should be readily available to any dermatologist prescribing methotrexate. As soon as overdose is suspected, serum should be collected for measurement of methotrexate levels and folinic acid should be administered intravenously.

In suspected cases of **Methotrexate overdose** or severe haematological toxicity consider treatment with **Folinic acid**. The initial dose should be at least 20 mg, given **intravenously**. Subsequent doses of 15 mg (which may be taken orally) should be given at **6 hourly** intervals until the haematological abnormalities are improved (**usually not more than 2-8 doses**). If serum methotrexate is measured, a dose of 20mg usually is sufficient for a methotrexate concentration of 0.5 micromoles/l or less.

Adequate hydration is essential to ensure maximal renal elimination and, in cases of massive overdose, alkalinisation of the urine with sodium bicarbonate may be required to prevent precipitation of methotrexate in the renal tubules. In patients with poor drug excretion or delayed drug absorption, methotrexate levels can remain dangerously elevated for several days after an overdose and folinic acid should be continued until it is certain that all methotrexate has been excreted. If plasma methotrexate levels are unavailable folinic acid should be continued until the blood count has returned to normal and the mucosae have healed. Early treatment may be life-saving. Every dermatologist using methotrexate should know how to manage overdose.

Synergy with other treatments

Most forms of topical treatment can be continued in a patient on methotrexate. Systemic immunosuppressive drugs and UV radiation are not usually administered concurrently with methotrexate.

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Oral Retinoids

The oral retinoid of choice in the treatment of psoriasis is acitretin. This is the carboxylic acid metabolite of etretinate, the first oral retinoid drug to be used for this disease. Acitretin is readily absorbed and widely distributed after oral administration.

Efficacy

Acitretin has been shown to be an effective agent when given alone for psoriasis, Goldfarb et al found a 66% clearance after 24 weeks, and Berbis et al found an 80% or greater clearance in a 12 week study. Acitretin is effective as a monotherapy, and can be expected to produce about 70% clearance in approximately 8 weeks.

Long term treatment with acitretin may be required as retinoids are only suppressive. Anecdotal evidence suggests that the therapeutic effect is maintained and treatment resistance does not occur.

Synergy with other treatments

Combination with PUVA treatment was found superior to PUVA combined with placebo, with regard to clearance time (47.8 versus 65.4 days), the number of exposures (13.7 compared to 19.9), and the number of patients remitting completely (94% compared to 65% at 10 weeks). The major advantage of combining acitretin with PUVA is the reduction in the dose of UVA, and some reduction in the daily dose of acitretin, to achieve clearance. On this basis, it may be expected that there will be a reduction in the long term side effects of both forms of treatment.

Safety, side-effects and patient acceptability

Acitretin therapy is associated with a large number of side effects and toxicity reactions.

Mucocutaneous and other minor adverse reactions: Acitretin causes mucocutaneous side effects in virtually all patients to whom it is administered in therapeutic doses. Drying and cracking of the lips, referred to incorrectly as cheilitis, may be expected in all after 2 - 4 weeks. For the majority of patients, this is a minor inconvenience that can be improved symptomatically by the use of a bland greasy application, such as white soft paraffin.

Dryness of the nasal, buccal and conjunctival mucosae occurs in a relatively small proportion. An increased rate of loss of scalp hair occurs in 20 - 30% patients, but is only severe enough to be noticeable and cause distress in a few women. Peeling of the skin of the palms and soles, and the development of areas of dermatitis, occurs in 5-50% of patients. Skin stickiness, skin and nail fragility, and itchiness are also seen in a minority of patients. Paronychia, and the development of curly hair, are other infrequent side effects. Musculoskeletal side effects, with arthralgia and myalgia, are uncommon.

As with all retinoid drugs, there is a high risk of teratogenicity if acitretin is administered during the first 3 months of pregnancy. As acitretin can be reverse metabolised to etretinate which has a long half life, pregnancy should be avoided for a period of 2 years after stopping acitretin. Numerous congenital malformations may occur, including Fallot's tetralogy, other cardiac defects, microcephaly, spina bifida and limb defects. Great care must be undertaken to ensure that all fertile women who are described acitretin understand the risk, that they are not pregnant from the start, and that they comply with secure contraceptive measures.

Elevation of liver enzymes is common, occurring in 20 - 30% patients. It is mostly of a minor degree, may be transient, and is generally of little significance. Hepatitis is rare, and maybe of the hypersensitivity, direct toxic, or cholestatic types. Modest elevation of plasma lipid levels occurs in up to 25% of patients, with increases in low density lipoproteins and decreases in high density lipoproteins. In individuals taking acitretin for psoriasis in the longer term, there is a risk of accelerated atherosclerosis if hyperlipidaemia persists. Those with elevated levels of lipids, should be given dietetic advice and, if necessary, lipid lowering agents prescribed.

Retinoid drugs possess the potential for bone toxicity, but it is uncertain to what degree that risk exists in those taking acitretin at the recommended dosage for periods of a few months to up to 2 years. Ossification of ligaments and tendons, bony spurs, and diffuse skeletal hyperostosis, has been reported in 86% of patients taking acitretin for 1 - 3 years at a dose of 10 - 75mgs per day, but adequate determination of the existence of these defects prior to therapy was not made. Premature epiphyseal fusion, and other bone abnormalities such as ossification of interosseous membranes, is rare.

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Ciclosporin

Ciclosporin is a highly effective and rapidly acting systemic treatment for psoriasis. This drug was first discovered in 1970, and was developed as an immunosuppressant for use in organ transplantation. The first controlled trial in psoriasis was published in

1986, and a license was granted in the U.K. for the treatment of severe psoriasis in 1992.

The main side effects are renal impairment and hypertension, both of which are largely reversible provided that guidelines regarding monitoring and dosage are followed. In other situations such as transplantation, the incidence of lymphoma is increased in patients receiving long-term ciclosporin. However, these individuals are much more intensively immunosuppressed than those taking ciclosporin for treatment of psoriasis.

Dosage regimens

For treatment of psoriasis the dose should not normally exceed 5 mg/kg/day and this is usually divided into two daily doses. Ciclosporin may be employed either as a maintenance treatment, using long term continuous therapy, or as a short course of treatment for 4 to 12 weeks, to induce remission, which might then be repeated later following relapse. Less severe cases are best treated with intermittent therapy which causes less toxicity and side effects. Patients with the more active disease require maintenance therapy and long-term continuous ciclosporin therapy may be appropriate in a subgroup of patients; however, duration of treatment should normally be kept below 2 years whenever possible. Treatment needs to be tailored to individual patients and when long-term continuous ciclosporin therapy is necessary, annual evaluation of glomerular filtration rate may be useful to accurately monitor renal function.

The starting dose ranges from 2.5 to 5 mg/kg/day. If improvement is not apparent after 2 weeks the dose can be increased by 0.5 to 1 mg/kg/day at fortnightly intervals provided that the maximum dose rate of 5 mg/kg/day is not exceeded. Once adequate improvement has occurred either the drug can be stopped in less severe cases or the dose can be reduced in steps of 0.5 to 1 mg/kg/day, at fortnightly intervals to determine the lowest dose at which adequate control of the psoriasis can be maintained. The maintenance dose required may vary over time with disease activity. The aim of maintenance treatment should not be to maintain the patient completely clear of psoriasis, but rather to keep the disease activity at a level tolerable for the patient.

Efficacy

The efficacy of ciclosporin has been demonstrated in double-blind, placebo controlled trials. The effect of the ciclosporin can be maintained by long-term treatment.

Response to ciclosporin has been reported for all the clinical variants and manifestations of psoriasis including erythrodermic psoriasis, generalised pustular psoriasis, palmoplantar pustulosis and acrodermatitis continua of Hallopeau.

Although ciclosporin is currently licensed for treatment of severe psoriasis, it has also been suggested that treatment of more moderate forms of chronic plaque psoriasis may be appropriate.

Safety and side effects

The most frequent problem requiring withdrawal of ciclosporin is renal impairment, which is related to dose and duration of treatment. Even short courses of treatment at the dose of 5 mg/kg/day may produce a measurable effect on renal function. This appears to be largely reversible provided that the recommended dose rate of 5 mg/kg/day is not exceeded and that the dose is reduced, and treatment stopped if required, to prevent the serum creatinine rising to more than 130% of baseline. After prolonged treatment nephrotoxicity will not be completely reversible. However, renal impairment does not become progressive after treatment is discontinued. Hyperkalaemia is a manifestation of renal impairment, which is occasionally problematic. Serum potassium should therefore be monitored in conjunction with the serum creatinine .

Treatment with ciclosporin results in an increase in blood pressure. Significant hypertension may develop at any time during treatment and this is probably a dose dependent effect. Hypertension resulting from ciclosporin therapy can either be treated or the dose of ciclosporin can be reduced. Nifedipine is the drug of first choice if it is considered necessary to treat hypertension. It should be noted that other calcium antagonists are known to increase the plasma level of ciclosporin.

An increase in serum bilirubin is often observed during ciclosporin treatment. Isolated increases in serum bilirubin do not usually require ciclosporin dose adjustment. Other side effects include myalgia, arthralgia, gastrointestinal disorders (nausea, abdominal pain and diarrhoea), gingival hyperplasia, headache, hypertrichosis, paraesthesiae and tremor. Nausea is most frequently encountered after the first few doses and usually resolves. Gum hypertrophy may

respond to improved dental hygiene or a reduction in dose. Hypertrichosis is often seen to some degree and may be a particular problem in female patients with dark hair. Ciclosporin can raise serum cholesterol and triglyceride levels and urate levels, and may also mildly impair glucose tolerance.

Infections, including herpes simplex, have not been a prominent problem during treatment of psoriasis. However, ciclosporin can be hazardous in patients who have suffered from hepatitis B or C.

The risk of malignancy developing as a result of long term immunosuppression is significantly increased. Although there is no doubt that the risk of diverse malignancies, including cutaneous tumours and lymphomas, is increased in transplant patients, this group undergo immunosuppression of a different order of magnitude to dermatological patients. Cutaneous malignancy may be a particular hazard because patients with psoriasis will often have received therapeutic ultraviolet irradiation. Squamous cell carcinomas have been reported in these circumstances.

Contraindications

These include patients with renal disease; hypertension; hyperlipidaemia; impaired glucose tolerance; active chronic infection or evidence of previous infection with hepatitis B or C; history of malignancy. Ciclosporin is not known to be teratogenic. Although its use cannot be recommended in pregnancy, it would seem preferable to using cytotoxic drugs, retinoids and perhaps PUVA. In the elderly, the usefulness of ciclosporin tends to be restricted by a lower renal reserve.

Drug interactions

Potassium-sparing diuretics may exacerbate ciclosporin-induced hyperkalaemia and should only be initiated with regular monitoring of U&E's.

St Johns Wort is known to decrease ciclosporin levels. Herbal medicines may have an effect on drug levels. Avoid concomitant use.

Ciclosporin should not be taken within one hour of grapefruit juice as this increases drug absorption

Numerous drugs affect the hepatic metabolism of ciclosporin by inhibiting or inducing cytochrome P450 3A and these may reduce the efficacy or increase the toxicity of cyclosporin. Important examples of drugs inhibiting ciclosporin metabolism are diltiazem, erythromycin,

itraconazole, and verapamil. Drugs, which may induce increased ciclosporin metabolism, include carbamazepine, phenytoin rifampicin and orlistat.

It is best to avoid ciclosporin, if possible, in patients requiring any other nephrotoxic drugs, including non-steroidal anti inflammatory agents (particularly diclofenac: Half dose of diclofenac if given concomitantly). An up to date reference list, such as that found in the British National Formulary, should always be consulted when prescribing concomitant systemic medication.

Ciclosporin can increase the risk of myositis with statins. Simvastatin can be used but not more than 10mg daily.

Monitoring

Before starting ciclosporin, blood pressure should be recorded and examination performed for any evidence of lymphadenopathy, malignancy or infection. Female patients should be encouraged to attend for a cervical smear if this has not been performed within the last three years. Serum creatinine should be measured to establish a baseline. Since this may vary considerably from day to day, it is recommended that two estimations be performed, at intervals of a few days, and the mean should be used as the baseline value. A baseline creatinine clearance is useful. Other useful investigations at baseline are liver function tests, serum electrolytes and urate, fasting blood sugar and lipid levels, and urinalysis.

Blood results should be repeated fortnightly for 8 weeks after achieving a stable dose and then monthly, After a period of six months, if the ciclosporin has been well tolerated, it is possible to extend the review interval to six or eight weeks in some patients.

Serum creatinine and electrolytes should be checked at each visit. Small reductions in glomerular filtration rate (GFR) in the normal kidney are not detected by monitoring serum creatinine. However, in subjects in whom renal function is already impaired, the creatinine rises much more promptly with small changes in the GFR. This investigation is therefore most sensitive in the circumstances where it is most important. Experience in the treatment of psoriasis suggests that changes in renal function are largely reversible after stopping treatment provided that the dose is reduced as required to prevent a sustained rise in serum creatinine of more than 30%. If there is a sustained rise in serum creatinine exceeding 30% above the baseline value the dose should be reduced by 0.5 to 1 mg/kg/day and review intervals should not exceed one month. If the creatinine has risen by more than 50% larger dose reductions may be required, and if the

creatinine fails to return to within 130% of baseline consideration should be given to use of an alternative treatment. Measurement of the GFR using radioisotope excretion studies is not essential.

Blood pressure should also be monitored at each review. Fasting serum lipids should be checked on treatment. It is probably not mandatory to monitor these after the first three months. At intervals of three to six months, complete medical examination is recommended particularly to seek evidence of neoplasia.

Patient acceptability

Ciclosporin is generally well tolerated. The reduction in disease activity is often rapid. The most significant side effects, hypertension and renal impairment, are asymptomatic in the early stages and other side effects are not usually troublesome.

Synergy with other treatments

It is likely that a certain level of dose sparing can be achieved by using topical treatment concomitantly with ciclosporin. Very satisfactory control of psoriasis can be achieved, at least in some patients, using a very low dose of ciclosporin, 2 mg/kg/day. Ciclosporin can be effective with relative dose sparing in combination with methotrexate or hydroxycarbamide. Greater care with monitoring is required if combining therapies.

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Hydroxycarbamide (Previously known as Hydroxyurea)

Hydroxycarbamide is a second line modality for the treatment of psoriasis and has been used since 1965. It is usually reserved for cases where other second line agents have failed or are contraindicated. The dose used has generally been 0.5 to 2.0g daily, give orally either as a single dose, or divided into two doses (morning and evening). Although only a single controlled trial has been performed, it is generally considered to be effective.

Hydroxycarbamide avoids the hepatotoxicity associated with methotrexate, and the nephrotoxicity associated with ciclosporin, and can therefore often be useful when other drugs are contraindicated, although it should be avoided, if possible, when renal function is markedly impaired. The main hazard is myelosuppression and careful monitoring of the full blood count is therefore required. It is recommended that the initial dose in adults should usually be 1g daily and this can be titrated, according to efficacy and toxicity, up to a maximum of 2g daily. Full blood count, including platelet and differential white cell counts, should be performed at least weekly for the first two months.

Efficacy

The use of hydroxycarbamide in the treatment of psoriasis has been confirmed in a double-blind, placebo controlled crossover trial. Each treatment period was 4 weeks, and the dose of hydroxycarbamide was 0.5g twice daily. Twelve subjects were included and 10 completed the protocol. Subjects and investigators considered that improvement had occurred during active therapy in 9 and 7 out of 10 cases respectively. Only one patient improved by either assessment during placebo treatment. The level of response was not quantified and no statistical analysis was presented.

Moschella and Greenwald reported a study in which 60 patients were treated intermittently with hydroxyurea (hydroxycarbamide), starting at the dose of 500mg twice daily. Patients who failed to respond to the initial dose were treated with 1.5g daily. During the first 6 weeks of treatment, 63% of the patients showed a good or excellent response, including some with erythrodermic and pustular psoriasis; a fair response was seen in another 10%. Patients in whom the drug was effective generally began to show some improvement within 2 to 3 weeks. In the majority of these patients the response was able to be successfully maintained by subsequent courses of treatment.

Layton et al. reported their experience of treating 85 patients, at doses of 0.5 -1.5g daily, over a period of eight years. Sixty percent of these patients cleared completely or nearly completely, and a further 20% showed partial clearance. The response was maintained in 52 by continuous therapy, for a mean of 16 months at the time of reporting. The reported duration of remission following cessation of hydroxycarbamide has varied from 24 hours to several months. Rebound of psoriasis after discontinuation has been occasionally reported.

Hydroxycarbamide has sometimes been helpful in treating generalised pustular psoriasis but results are variable.

Synergy with other treatments

Hydroxycarbamide has been used safely and effectively in combination with ciclosporin, more caution is necessary in combination with other potentially myelosuppressive drugs

Safety, side-effects and patient acceptability

The main concern regarding toxicity of hydroxycarbamide has been over myelosuppression, which may manifest as megaloblastic anaemia, thrombocytopenia or leukopenia. Haematological abnormalities are particularly frequent with this drug. Layton et al reported significant blood changes in 35% of their patients and, in one report, macrocytosis and a reduced red cell count, although not anaemia, were seen in 4 of 5 patients treated. These side effects may develop after several months of treatment. They have generally been reversible after discontinuation of the drug. Since hydroxycarbamide is largely excreted in the urine, extra caution is required if renal function is impaired. It may occasionally cause fever. Cutaneous side effects of hydroxycarbamide include partial alopecia, increased pigmentation, scaling, atrophy, nail changes, erythema of

the face and hands, and a lichenoid eruption. Hydroxycarbamide is a cytotoxic drug with potential for teratogenic effects and is best avoided in women of child-bearing age.

Monitoring

It is recommended that patients should have their full blood count, including platelet count and differential white cell count, checked prior to commencing the drug and, at least, weekly intervals for at least the first six weeks. Subsequently, the intervals between haematological assessments may be gradually extended, provided there is no cause for concern. The maximal interval should not exceed three months. Serum creatinine and liver function tests should also be monitored. It would also seem prudent to examine patients every six months for evidence of malignancy and to advise females to attend, when called, for routine cervical smears.

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Fumaric acid esters (FAE)

Fumaric acid esters are marketed in Germany and constitute a mixture of dimethylfumarate and calcium, magnesium, and zinc salts of monoethyl hydrogen fumarate. As such it has to be imported and used on a named patient basis in the UK, which renders this a more expensive therapy than ciclosporine or methotrexate. It is presented as 2 strengths initial and high strength which are gradually increased within the patients' tolerance according to the schedule summarised in the table. Dimethylfumarate (DMF), the main

ingredient of the marketed mixture, is the active compound and is now demonstrated as efficacious in a phase III multicentre trial. Although not yet commercially available this single compound has fewer side effects and will be more readily licensed as a single entity drug.

Fumarates are thought to work by shifting a Th1-type cytokine response to a Th2-type pattern whereby IL-10 inhibits Th1 cytokines IL-2 , IL-12 and IFN gamma and by inhibiting translocation of nuclear factor kappa B (NF-κB).

Patients tolerating the therapy can expect a 75% reduction in PASI in 4 months. However, all studies of the mixture of esters have a high dropout rate due to gastrointestinal complaints diarrhoea, stomach cramps and tenesmus that occur in up to 60% of patients and flushing in 30% of patients, which is worse at the onset of therapy. Headaches may be associated with sudden flushing. The frequency of flushing is greatest at the onset of therapy and decreases with prolonged treatment time. Both adverse events lead to drug withdrawal in about 7% of patients

Laboratory monitoring is required monthly particularly for lymphopenia (less than 20% of white cells) in 75% of patients is usually mild and plateaus. Transient eosinophilia is observed in 14-25% and lymphocytopenia was observed in 76%. Liver enzymes are frequently raised (25% of patients) and reverse on stopping therapy, raised cholesterol (17%), increase in triglycerides (8%), raised serum potassium (15%) and increase in serum creatinine (4%) and although proteinuria (11%) may occur there is no evidence of significant nephrotoxicity as seen with ciclosporin. There are no reports of severe long-term toxicity or development of cancer or a higher susceptibility for bacterial infections, thus making FAE a safe regimen, compared to other agents

Number of tablets of fumaric acid esters to be taken for treatment of psoriasis

Week	Morning	Noon	Evening	Preparation
1	1	-	-	A

2	1	-	1	A
3	1	1	1	A
4	1	-	-	B
5	1	-	1	B
6	1	1	1	B
7	2	1	1	B
8	2	1	2	B
9	2	2	2	B

A, low strength; B, high strength

A reduction in FAE dose is required in the following situations: decrease in leucocyte count to below $3.0 \times 10^9/L$; decrease in lymphocytes to below $0.5 \times 10^9/L$; persistent eosinophilia $\geq 25\%$; rise in serum creatinine 30% above baseline; development of proteinuria. If the abnormal parameter improves, treatment with FAEs can be continued at a reduced dose. In case of a persistent abnormality or a further deterioration, FAEs must be withdrawn.

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Mycophenolate mofetil

Myconphenolate mofetil is an anti-metabolite immunosuppressive developed for organ transplantation. No randomised trials have been performed in psoriasis but several reports indicate a beneficial effect. PASI decreased within 3 weeks by 40–70% in seven of 11 patients, and by 25–39% in three of 11. It appears less efficacious than ciclosporin but can be combined with low dose ciclosporin.

Usually myconphenolate is commenced at a lower dose of 250-500mg twice daily and gradually increased to 1g twice daily. In transplantation higher doses are associated with increased toxicity but no further efficacy. Response in psoriasis does not appear to be a result of pharmacokinetic effects. Once response is observed the dose can often be reduced.

Initial monitoring is with weekly FBC for one month then fortnightly for two months and monthly thereafter. Women of childbearing potential receiving myconphenolate mofetil should be advised to use effective contraception prior to, during and for six weeks following discontinuation of therapy. Patients discovered or planning to become pregnant should be referred to the specialist at the earliest opportunity. **Breastfeeding:** women treated with myconphenolate mofetil should not breastfeed.

Myconphenolate interacts with cholestyramine and antacids (reduced absorption). 50% of patients experience gastrointestinal upset, nausea, cramps, diarrhoea. Rarely perforation or haemorrhage or pancreatitis occur. Bone marrow suppression is an important adverse effect with leukopenia in 5% of patients

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Azathioprine

See separate BAD guidelines on azathioprine therapy on this site

Biological interventions

See separate BAD guidelines on biological therapies including infliximab, etanercept and efalizumab on this site