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Review

A systematic review of treatments for severe psoriasis

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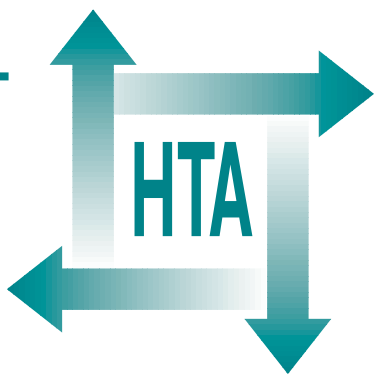
Health Technology Assessment
NHS R&D HTA Programme



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A systematic review of treatments for severe psoriasis

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NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

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Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.

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Contents

Glossary and list of abbreviations

BBUVB	broadband ultraviolet B (290–320 nm)
BP	blood pressure*
BSA	body surface area*
CI	confidence interval
CSA	cyclosporin A*
DB	double-blind*
DMFAE	dimethylfumaric acid ester*
EDEN	European Dermato-Epidemiology Network
Fumarates	esters (mixed) of fumaric acid
Goeckerman regimen	combination treatment with phototherapy and coal tar
HLA	human leucocyte antigen
IL	interleukin
Ingram regimen	combination treatment with phototherapy and dithranol
J	joule
MED	minimum erythema dose
MEFAE-Ca	calcium salt of monoethylfumaric acid ester*
MEFAE-Mg	magnesium salt of monoethylfumaric acid ester*
MEFAE-Na	sodium salt of monoethylfumaric acid ester*
MEFAE-Zn	zinc salt of monoethylfumaric acid ester*
MOP	methoxypsoralen
MPD	minimal phototoxic dose
NB	not blinded*
NBUVB	narrowband ultraviolet B (311 nm)
NFAT	nuclear transcription factor of activated T cells
NICE	National Institute for Clinical Excellence
NR	not reported*
OHFAE	octyl hydrogen fumaric acid ester*
OR	odds ratio
PASI	Psoriasis Area and Severity Index
PNBUVB	psoralen plus narrowband ultraviolet B
PSI	Psoriasis Severity Index (a modified PASI)
PUVA	psoralen plus ultraviolet A
RCT	randomised controlled trial
RD	rate difference (also known as risk difference)
RePUVA	retinoid plus psoralen plus ultraviolet A
Retinoid	synthetic derivative of vitamin A
SB	single-blind*
SD	standard deviation
SEM	standard error of the mean
SF-36	Short Form with 36 Items
Th	T-helper
TMP	trimethylpsoralen*
UVA	ultraviolet A (320–400 nm)
UVB	ultraviolet B (290–320 nm)
VAS	visual analogue scale*

* Used only in tables or figures

Executive summary

Objectives

This systematic review of the evidence base was carried out to compare the effectiveness of currently available treatments for severe psoriasis and to identify areas in need of further research.

Methods

Data sources

Systematic searches of MEDLINE, EMBASE, the Cochrane Controlled Trials Register and the European Dermato-Epidemiology Network were undertaken. Report authors and drug manufacturers were also asked for information. The initial searches identified 2873 citations about psoriasis treatment.

Study selection and assessment of validity

Studies were considered eligible if they were randomised controlled trials (RCTs) of interventions for the treatment of moderate-to-severe chronic plaque psoriasis. Reports concerned exclusively with palmoplantar pustular psoriasis, guttate psoriasis or psoriatic arthritis were excluded. Relevant studies in any language were accepted. Studies were excluded if they contained data that had already been published elsewhere or if insufficient data were reported for analysis. Decisions about inclusion were made by two reviewers.

Data extraction

Data concerning all outcomes of interest were extracted from all eligible studies and entered into spreadsheets.

Data synthesis

Although the Psoriasis Area and Severity Index (PASI) appeared to be an attractive, objective measure of treatment success, it was not used by all investigators. When the PASI was used, the results were not handled in a consistent manner. Nevertheless, in most cases, the PASI was used as the main outcome measure for this review. Many trials reported the rates of treatment success, and there appeared to be a broad consensus about such criteria. Results are therefore presented as success rate differences and displayed as forest plots. When homogeneity across trials could be demonstrated, pooled rate differences are also shown.

Results

In total, 111 RCTs were included in this review. Within each intervention group, there was considerable heterogeneity, including the drug dose, duration of treatment, baseline severity of disease, success criterion and mix of patients (by psoriasis subgroup). In trials of phototherapy, an additional source of heterogeneity was the mix of patients by skin type. Drug formulation and patient compliance may also have played a role.

This systematic review attempted to be an exhaustive examination of current evidence and RCTs; however, it was often found that the important outcomes had not been measured. In addition, there were few comparisons between systemic therapies and relatively few combination studies, which is not a true reflection of clinical practice. Most studies were short-term and inadequately reported side-effects, long-term complications and the costs of treating severe psoriasis.

Cyclosporin

There is strong RCT evidence to support the use of cyclosporin, which was usually effective in inducing the remission of psoriasis when used in the dose range of 2.5–5.0 mg/kg/day. Doses above 5.0 mg/kg/day were associated with increased side-effects, which precluded any dose-related gains in efficacy. Maintenance treatment required a dose of 3.0–3.5 mg/kg/day, and although relapses were likely if the drug was given intermittently (as opposed to continuously), intermittent treatment appeared to be safer.

Retinoids

RCTs found retinoids to be moderately effective as monotherapy at doses of 75 mg/day or 1 mg/kg/day. Acitretin was as effective as etretinate, which was less effective than cyclosporin.

There is good RCT evidence to support the use of combination treatment with a retinoid and psoralen plus ultraviolet A (PUVA). This combination was more effective than retinoid therapy alone and had the advantage of lowering the cumulative ultraviolet A (UVA) dose.

Methotrexate

There is a lack of RCT evidence to support the use of methotrexate. Despite this lack of RCT data, it is important to note that open and retrospective studies suggest that methotrexate is effective in inducing and maintaining remission in patients with severe psoriasis.

Photochemotherapy and phototherapy

PUVA using oral psoralen (8-methoxypsoralen, 0.6–1.0 mg/kg) was found to be effective in clearing psoriasis. PUVA using topical psoralen ('bath PUVA') was equally effective. UVA alone, however, did not clear psoriasis.

Ultraviolet B (UVB) phototherapy was effective in clearing psoriasis. Narrowband UVB (311 nm) offered the possibility of clearance with fewer episodes of erythema and a lower cumulative dose of UVB, compared with broadband UVB.

It is not yet known how narrowband UVB compares with PUVA, based on the RCT evidence. PUVA or UVB in combination with retinoids appeared to be more effective than either treatment alone. No evaluable RCTs compared the effects of adding topical tar to either PUVA or UVB with PUVA, or to UVB alone. PUVA was as effective as daily dithranol in clearing psoriasis, but there were no trials that evaluated the effects of adding PUVA to dithranol treatment.

Combination treatment using phototherapy or photochemotherapy with a vitamin D_3 analogue (e.g. calcipotriol) was more effective than either treatment alone. Phototherapy or photochemotherapy combined with a topical steroid was also more effective than either treatment alone.

Hydroxyurea

There is some evidence that individual patients may respond to treatment with hydroxyurea, based on the one eligible RCT, which was not obtained by our standard search strategy.

Fumarates

Oral fumaric acid ester (fumarate) therapy was found to be an effective systemic treatment for psoriasis. Based on the evidence, dimethylfumarate appears to be the principal active component.

Azathioprine

No RCTs were found regarding the use of azathioprine in the treatment of psoriasis, and it is now rarely used.

Sulphasalazine

Only one RCT assessed the use of sulphasalazine in the treatment of severe psoriasis. This trial found that sulphasalazine was a moderately effective and potentially long-term treatment. However, the drug's efficacy was offset to a degree by patient intolerance and side-effects, particularly nausea, vomiting and rashes.

Costs and cost-effectiveness

Several analyses of the costs of psoriasis treatment have been published, but none has so far provided a sound basis for decision-making or for the formulation of prescribing guidelines in the UK. Nevertheless, these studies have identified some of the problems associated with economic analyses of psoriasis treatment. Studies are needed to establish the cost-effectiveness and cost–utility of all the treatments for severe psoriasis in the UK.

Conclusions

Implications for healthcare

Although the availability of RCTs has dictated that this report deal exclusively with systemic treatments and phototherapies, it is important to be aware that patients with severe psoriasis are frequently treated by means of inpatient or day-treatment centre management (e.g. topical dithranol combined with UVB phototherapy), for which there are no published RCTs. Thus, the recommendation of systemic therapies should not preclude traditional inpatient or day-treatment centre management.

The findings show that there is firm RCT evidence of the effectiveness of some systemic treatments for severe chronic plaque psoriasis, specifically:

- cyclosporin
- systemic retinoids (acitretin and etretinate), especially in combination with PUVA
- photochemotherapy and phototherapy (PUVA, broadband UVB and narrowband UVB)
- combinations of topical vitamin D_3 analogues and topical steroids with either photochemotherapy or phototherapy
- fumarates.

There is a lack of firm RCT evidence for other treatments for severe chronic plaque psoriasis, including:

- methotrexate, although this widely used treatment was introduced prior to the advent of RCT evidence
- hydroxyurea
- azathioprine
- sulphasalazine, although one RCT showed moderate efficacy.

Recommendations for further research

High-quality RCTs are needed in a number of areas; however, before further trials are started, two critical steps should be taken.

1. Outcome measures of relevance to clinicians and patients should be developed to assess therapeutic response in psoriasis.
2. A definition of 'severe psoriasis' should be developed. If possible, such a definition should be all-encompassing and holistic in its outlook, incorporating not only the clinical severity of psoriasis but psychosocial disability and historical disease behaviour.

The following RCTs of treatments for severe psoriasis could perhaps be justified to compare:

1. cyclosporin versus methotrexate
2. systemic therapy/phototherapy versus inpatient and/or day-treatment centre management
3. acitretin versus methotrexate, in a long-term study
4. fumarates versus methotrexate, in both short- and long-term studies
5. narrowband UVB versus PUVA, in both short- and long-term studies
6. hydroxyurea versus placebo
7. azathioprine versus placebo
8. sulphasalazine versus placebo.

There is justification for performing economic evaluations, including more formal cost-effectiveness and cost–utility studies of the various treatment options, particularly in comparison with inpatient and day-treatment centre management. All future trials should include an economic evaluation and be of sufficient duration for the impact on patients to be determined.

Chapter 1
Introduction

Definition of psoriasis

The term 'psoriasis' was first used by Galen and derives from the word '*psora*', to itch. It is probable that Galen originally described seborrhoeic dermatitis and that psoriasis itself was grouped with leprosy under the descriptive '*lopoi*'.[1] The inability to distinguish between leprosy and psoriasis persisted from the time of Hippocrates (400 BC) through the Middle Ages, when lepers and, by association, psoriatic individuals were both shunned and harshly treated by society. The founder of modern dermatology, Robert Willan, is credited with the first accurate description of psoriasis in 1808.[2] However, it was not until 1841 that Hebra finally differentiated leprosy from psoriasis.

Even 160 years later, the diagnosis of psoriasis is still a clinical one and a process that is entirely reliant on categorising cutaneous features and patterns as being most consistent with those of psoriasis. There are no diagnostic haematological, biochemical or serological tests, although histological assessment of skin biopsy may at times be helpful. It is likely that modern molecular genetics will provide the means to accurately diagnose psoriasis and possibly determine further genotypic and subtle phenotypic subsets of the disease. This having been said, the diagnosis of psoriasis is usually straightforward for the dermatologist. Cases of uncertainty involve erythroderma (> 90% skin involvement), and the differential diagnoses may include cutaneous T cell lymphoma, atopic dermatitis, drug eruptions and pityriasis rubra pilaris, and when the scalp alone is affected, seborrhoeic dermatitis.

Chronic plaque psoriasis vulgaris is the commonest form of the disease, and its cutaneous manifestations are the most representative. A plaque of psoriasis is sharply demarcated from surrounding uninvolved skin, with no gradation as seen, for instance, in atopic dermatitis.[3] Most of the plaques are palpable, but this feature may range from the barely perceptible to the thick and craggy so-called 'rupioid pattern'. The individual plaques are erythematous, varying in the intensity of colour from pink to beefy red, depending on anatomical site (redder on lower extremities), and they are surmounted by a variable amount of scale. The scales are individually white or cream in colour, but *in situ*, on a plaque, they appear silver due to the reflection of light from air trapped between the loosely adherent scales. Thus, for the assessment of psoriasis severity, the features of induration, erythema and scale are the three descriptive features.

Although the epidermis is greatly thickened (acanthosis) in a plaque of psoriasis, gentle scraping of adherent scale, using a wooden spatula, will rapidly reveal pinpoint bleeding (the Auspitz sign). This clinical phenomenon is unique to psoriasis and occurs because of epidermal thinning above highly vascular dermal papillae. Active plaques are frequently encircled by a ring of white vasoconstricted skin (the Woronoff ring), probably resulting from a local overproduction of prostaglandins. Individual plaques of psoriasis are dynamic in that they are usually moving outwards. Laser Doppler flowmetry allows assessment of plaque movement into as yet uninvolved skin. In some circumstances, the speed of movement is rapid in that the centre of a plaque clears, leaving an annular lesion, which is occasionally confused with tinea corporis. Psoriasis may occur in sites of epidermal trauma or pressure, for example, under tight clothing (the Köbner phenomenon).

Individual plaques vary greatly in size, from 'guttate' lesions of 2–3 mm in diameter to plaques covering the whole lumbosacral area (i.e. > 20 cm in diameter). Irrespective of size, individual plaques are macroscopically identical. The most common sites of involvement are the extensor aspects of elbows and knees, the scalp, and lumbosacral region; however, any skin surface may be affected. Morphology varies according to site. In flexural sites, perineum, sub-mammary and axillae, the occlusive environment reduces induration and scaling but accentuates erythema. Scalp psoriasis rarely strays beyond the hairline and may occur in a seborrhoeic distribution in nasolabial folds, eyebrows and post-auricularly (so-called 'sebopsoriasis').

The chronic plaque variety accounts for 85–90% of the cases of psoriasis, and this systematic review

focuses on the treatment of severe cases of this form of psoriasis. Very severe plaque psoriasis involving more than 90% of the skin surface area is termed erythroderma. For completeness, other clinical patterns of psoriasis include: (a) guttate (from the Latin *gutta*, a droplet) – a sudden shower of small lesions (2–3 mm in diameter) in a centripetal distribution, usually occurring in childhood and predated by a streptococcal pharyngitis or tonsillitis; (b) generalised pustular psoriasis (von Zumbusch) – painful erythema studded with monomorphic sterile pustules, which often occurs following the withdrawal of systemic corticosteroids; (c) palmoplantar pustular psoriasis – sterile pustules fading to brown on a scaled, erythematous background on palms and soles; (d) acrodermatitis continua of Hallopeau – pustular psoriasis localised to a single digit; and (e) impetigo herpetiformis – a rare pustular form of psoriasis occurring solely in pregnancy.

The nails, any number, are affected in approximately 50% of cases of psoriasis, with the clinical manifestations including thimble-like pitting, onycholysis (separation of the nail from the nail bed) and dystrophy. Pustular forms of psoriasis are more likely to be associated with nail disease. To complete the clinical picture, approximately 10% of patients with psoriasis also suffer from an inflammatory polyarthritis – psoriatic arthritis. This condition may manifest a variety of clinical patterns, which include oligoarthritis, psoriatic spondylitis, asymmetrical polyarthritis, arthritis mutilans and 'rheumatoid' polyarthritis. The most characteristic clinical features that aid differentiation from rheumatoid arthritis are asymmetry, the involvement of distal interphalangeal joints and the absence of circulating rheumatoid factor (sero negative arthritis).

Prevalence, genetics and triggers

Information about the prevalence of psoriasis is incomplete, probably because of the absence of definitive diagnostic tests and the suggestion that many patients with mild forms of psoriasis do not consult doctors for advice on treatment. Thus, the true prevalence is probably higher than accepted statistical data indicate. Additionally, because psoriasis is a disease that may present at any age and is dependent on environmental triggers, it is important to be aware that the cumulative prevalence of the phenotype will approach the prevalence of the genotype only in the elderly population. Good population-based studies of psoriasis prevalence are surprisingly scarce, but the accepted rate in the UK is 1–2%. Worldwide, there is variance around this figure, with psoriasis being most common in the Faroe Islands (2.8%) and rare in native Americans (0.5%). On this basis, approximately 1.2 million people in the UK have psoriasis – a significant disease burden and more common than rheumatoid arthritis.

Males and females are affected equally, although there is a significant female preponderance in the palmoplantar pustular subtype, and unlike atopic dermatitis, psoriasis is not social class linked. The mean age of onset is 28 years: at age 29 years for men, with an earlier onset of 26 years for women. There are two peaks of psoriasis onset: 16–21 years of age for type I psoriasis (75% of patients) and 55–60 years for type II psoriasis.[4] Psoriasis can present at any age, from 1 to over 100 years!

Psoriasis is usually chronic and persistent, although 50% of patients may enter spontaneous remission for varying periods of time.[5] Patients with psoriasis are significantly more likely to suffer from diabetes mellitus, inflammatory bowel disease,[6] hypertension and obesity, and are less likely to suffer from asthma, atopic dermatitis and urticaria than individuals in a control population.[7] Surveys, particularly in Scandinavia, indicate that the risk of developing psoriasis is 0.28 if one parent has psoriasis and 0.65 if both parents are affected.[8]

Approximately one-third of patients with psoriasis have a first-degree relative with the disease. Twin studies reveal concordance of 71% for monozygotes and 23% for dizygotes.[9] This observation implies that environmental triggers are important and, when in concert with the predisposing genotype, will lead to phenotypic expression of psoriasis. These observations have led to immense growth in research into the molecular genetics of psoriasis. Human leucocyte antigen (HLA) associations are particularly strong: 80% of patients with type I psoriasis are HLA-Cw6 positive, as are 100% of patients with guttate psoriasis. Molecular genetic research to date indicates that psoriasis is polygenic, with defined loci on chromosomes 6p, 17q, 4q and 1q, which have been named psoriasis genes 1, 2, 3 and 4, respectively.[10–12] Putative loci are present on chromosomes 2p, 6q, 8q, 16q and 20p. It is likely that many more gene associations will be described in the next 5–10 years and that what we currently call psoriasis may turn out to be a heterogeneous group of diseases linked only by similar patterns of skin pathology.

Environmental triggers for psoriasis are: (a) infection, particularly by group A β-haemolytic streptococcus, which is linked to guttate psoriasis,[13] and by human immunodeficiency virus infection;[14] (b) stress, with 60% of patients reporting that stressful life events may cause their disease to flare up, and it appears likely that acute-on-chronic stress is a key determinant; (c) drugs, including β-adrenergic receptor blockers, anti-malarial drugs, non-steroidal anti-inflammatory drugs and lithium, as well as withdrawal of glucocorticosteroids; and (d) alcohol, which may produce a flare-up in some patients. Diet has no proven effect on psoriasis.

Pathogenesis

The three main histological features of a psoriasis plaque are: (a) abnormal epidermal keratinocyte hyperproliferation and differentiation; (b) dermal vascular proliferation; and (c) a T cell-predominant inflammatory infiltrate of the dermis and epidermis. It is well accepted that psoriasis is a T cell-mediated disease, most probably autoimmune in origin.[15] The autoantigen is unknown, but speculative candidates include epidermal proteins such as keratin 17.[16] T cells may be induced to migrate preferentially to skin via activation by superantigens at distant sites, for instance, in tonsillar mucosa or peripheral blood. The T cell hypothesis is strengthened considerably by the efficacy of T cell-targeted approaches to psoriasis therapy, which include cyclosporin[17] and an interleukin 2 (IL-2) fusion toxin.[18] Within the epidermis, $CD8^+$ T cells predominate, whereas the dermal infiltrate is composed mainly of $CD4^+$ T cells.[1] Within the plaques, a T-helper 1 ('Th1') profile of cytokines predominates (i.e. interferon-γ, IL-2 and IL-12) at the expense of Th2 cytokines (e.g. IL-4, IL-5 and IL-10).[15] This local imbalance of the cytokine milieu gives mechanistic credence to the clinical observation of the relative scarcity of Th2 diseases (e.g. asthma, atopic dermatitis and urticaria) occurring in conjunction with psoriasis. Logically, discoveries of key pathogenetic pathways in psoriasis will lead to future targeted therapies.

Complications of psoriasis

The very nature of psoriasis, being chronic and incurable, indicates that its major impact on society is through morbidity. Indeed, very few people directly die from psoriasis. Suicide may result from depression about having to live with psoriasis. Undoubtedly, psoriasis should be viewed as a complex disability. Quality of life studies[19–22] have helped to put this handicap into perspective. The Sickness Impact Profile[20] demonstrates that patients with psoriasis have a quality of life that is impaired to a level analogous to that of individuals with angina or hypertension, although not to the level of those with cardiac failure. Other quality of life measures include the Psoriasis Disability Index and Psoriasis Life Stress Inventory, which help to determine further the poor quality of life suffered by such patients. There appears to be little correlation between the psychological stress caused by psoriasis and the clinical extent of the disease.[21] For most patients, the key life stressor is avoidance coping, that is, avoiding situations in which people may comment adversely about the patient having psoriasis (e.g. at public swimming baths). A second stressor is derived from the experience of being evaluated on the basis of their skin condition. Absence from work is often a direct result of severe psoriasis; for instance, psoriasis is a bar to entry into the armed forces, and in many cases (34%), an individual's inability to gain work is blamed on psoriasis.

Willingness to pay is important in determining the utility of treatments for non-fatal diseases such as psoriasis. In one study, patients were willing to spend 2–3 hours daily applying treatment if it would guarantee normal skin.[19] Patients with psoriasis also stated that they would be willing to spend up to £10,000 for a cure of their disease. Dissatisfaction with medical treatments for psoriasis has induced large numbers of patients to pay significant sums of money for alternative therapies, most of which are totally ineffective.[23] Many topical treatments are cosmetically unacceptable and time-consuming to use, and 40% of patients are willing to use systemic therapy even if there are side-effects.[24] Pharmaceutical companies are increasingly factoring pharmacoeconomic and quality of life measures into the design of studies of new treatments for psoriasis.

Most cases of psoriasis are mild to moderate in clinical severity and can be satisfactorily treated in a primary care setting; it is estimated that 75% of patients fall into this category. Patients are referred to the secondary care sector only if their psoriasis is too widespread or severe to be adequately treated with topical agents, if they are resistant to and/or suffer side-effects from topical therapy, or if they wish further referral despite adequate response. The assessment of psoriasis severity is not an exact science, and the definition of 'severe' will inevitably differ between dermatologists and patients. If one adheres to strict clinical criteria, then severe psoriasis could be defined as

psoriasis affecting ≥ 20% of the skin surface area or with a Psoriasis Area Severity Index (PASI) value* of > 10.[25] These criteria are strict and measurable. Other scoring systems have been developed that encompass a global score, usually from 0 (no psoriasis) to 7 or 8 (very severe psoriasis), or that run through gradings such as mild and moderate. Understandably, this type of scoring is a subjective assessment or gestalt. It is important to realise that difficult-to-treat or severe psoriasis does not necessarily equate with extent of disease. For instance, a patient with psoriasis of relatively minimal extent may be severely psychosocially disabled by the disease[21] and have unrealistic expectations of cure or response to treatment. Another patient with moderate disease may have failed and/or suffered side-effects from a variety of treatments. For the purposes of this review, the definition of severe psoriasis is a clinical one applied to chronic plaque/ erythrodermic disease. It is very likely that, as we move towards treating patients according to a holistic approach (i.e. as individuals), then the definition of 'severe' will change to a more realistic view and incorporate clinical extent, psychosocial disability and historical response to treatment.

Treatment of severe psoriasis

The management of patients with psoriasis is based on the premise that the working clinical diagnosis is correct. All patients, irrespective of disease severity, should be counselled about psychosocial disability and informed that psoriasis is neither contagious nor malignant, diets are unhelpful and the disease is not an allergic process. An integral component of the consultation is to ensure that patients are aware that treatment is suppressive at best and not curative. There is a perceived need for more effective therapies for psoriasis. A recent survey indicated that only 14% of patients believed that current treatments could be classified as effective. For topical treatments, the preparations available are often cosmetically unacceptable (due to smell, texture and staining) and are time-consuming to use; as a consequence, compliance is on the order of only 39%. Patients are less likely to comply with therapy the more severe their psoriasis (as judged by clinical grading) and the younger they are.[24] In the UK, most cases of psoriasis can be treated solely with topical preparations – so-called 'first-line' therapy.[3] It is unlikely that severe psoriasis can be satisfactorily managed on an outpatient basis solely with topical therapy.

First-line therapy

In most instances, ointment formulations are more effective than creams but are less cosmetically acceptable. For many patients, it is worth prescribing both cream and ointment formulations of an active agent (if available): a cream for use in the morning before going to work and an ointment for the night-time. The aim of all treatment should be to suppress symptoms, and the patient should be re-examined at least 6 weeks after starting a new therapy. This follow-up encourages compliance, and the doctor can assess the efficacy of the new intervention.

Emollients

Emollients, such as emulsifying ointment or any of an array of 'over-the-counter' and prescription preparations, are advisable for any patient with psoriasis. Emollients reduce desquamation, may limit painful fissuring and can act as an anti-pruritic. Emollients are best applied immediately after bathing or showering. The efficacy of bath emollients is less certain. Keratolytics, normally consisting of an emollient such as white soft paraffin to which salicylic acid (usually 5%) has been added, are helpful for descaling plaques preparatory to treatment with more active topical treatments.

Coal tar

Coal tar has been a standby of psoriasis treatment for most of this century. Crude coal tar contains approximately 10,000 moieties – it appears that the more refined and cosmetically acceptable the coal tar, the less active it is. Coal tar preparations of 0.5–5% are probably as effective as stronger 25% formulations. These preparations can be made up in white or yellow soft paraffin and applied twice daily to plaques. Treatment is usually begun with 0.5% coal tar and the concentration increased cautiously, dependent on efficacy and local irritation. Proprietary, refined coal tar preparations are frequently combined with 1% hydrocortisone.

* $PASI = 0.1(E_h + I_h + D_h)A_h + 0.3(E_t + I_t + D_t)A_t + 0.2(E_u + I_u + D_u)A_u + 0.4(E_l + I_l + D_l)A_l$.

Erythema (E), induration (I) and desquamation (D) are assessed according to a 4-point scale: 0, no psoriasis; 1, slight; 2, moderate; 3, marked; and 4, very marked. The various sites are: h, head; t, trunk; u, upper limbs; and l, lower limbs. In terms of the skin area (A) of plaques, a numerical value is given based on the extent of the lesions at the specified sites: 1, < 10%; 2, 10–29%; 3, 30–49%; 4, 50–69%; 5, 70–89%; and 6, 90–100%.

Dermatologists often compound crude coal tar with keratolytics and corticosteroids; one such popular compound is 5% crude coal tar, 5% salicylic acid and 25% potent corticosteroid ointment in base ointment to 100%.

Although the mechanism of action of coal tar is poorly understood, it is a keratolytic and probably possesses anti-inflammatory and anti-proliferative effects.

The most common side-effects of topical coal tar are irritation of uninvolved skin, folliculitis (inflammation of hair follicles), smell and staining of clothing. Consequently, compliance may be a problem. Although occupational exposure to coal tar is a well-known risk for the development of skin cancer, there is no evidence that this is true for coal tar products used in the treatment of psoriasis. Experimental studies have demonstrated the presence of polycyclic aromatic hydrocarbons in the urine of patients using coal tar-containing shampoos, but there is no evidence that coal tar-containing creams or shampoos cause either skin or internal cancers.

Dithranol (anthralin)

Dithranol is one of the oldest treatments available for psoriasis and, when used in conjunction with ultraviolet B (UVB) phototherapy, it is the gold standard for inpatient or day-treatment centre management of psoriasis (the Ingram method). Its main side-effects are irritation/burning of uninvolved skin coupled with purple–brown discolouration of skin, clothes, bathroom fittings, etc. Newer microcrystalline formulations of dithranol may be less irritant and more cosmetically acceptable. The mechanism of action of dithranol is most probably a direct anti-proliferative effect on epidermal keratinocytes. As with coal tar, its use is limited by cosmetic unattractiveness.

Dithranol treatment can be either applied by nurses (at inpatient or day-treatment centres) or self-administered (so-called 'short-contact' therapy). Nurse-applied dithranol is made up as 0.1–2.0% in zinc and salicylic acid (Lassar's) paste, which is applied to each plaque and left in place under stockinette gauze for up to 24 hours.

The effectiveness of outpatient, self-administered (short-contact) dithranol therapy is highly dependent on patient motivation and thus compliance. The cream or ointment formulation of dithranol is applied carefully to individual plaques (not flexures or face) and left *in situ* for 10–60 minutes prior to washing off. Proprietary dithranol preparations, which are available in 0.1–2.0% strengths, are gradually increased in concentration to a maximum of 2.0%, according to tolerance.

Topical corticosteroids

Due to the inherent cosmetic acceptability of most commercially formulated corticosteroid products, they have a high rate of patient compliance. However, this compliance and their efficacy are mitigated by potential side-effects, if used without adequate supervision. Topical corticosteroids should not be used for large areas of psoriasis and are best reserved for sites such as the hands, feet, flexures, genitalia, face and scalp. Recalcitrant psoriasis, particularly on the hands or feet, usually requires treatment with a potent corticosteroid, sometimes under plastic occlusion. Potent corticosteroids are generally required for the treatment of most plaque psoriasis, whereas flexures, face and genitalia should be treated only with mild-potency corticosteroids. Topical corticosteroid treatment always requires careful medical supervision; potent corticosteroid use should be limited to 2 weeks maximum, and no topical corticosteroids, apart from 1% hydrocortisone, should be used on a regular basis for more than 4 weeks without review.

The local side-effects of corticosteroid use include skin thinning, striae (stretch marks), telangiectasia (dilated skin capillaries) and rapid relapse (sometimes a rebound to a pustular form). Systemic side-effects may include Cushing's syndrome (hypercortisolism). A unique side-effect of topical corticosteroid use is that of tachyphylaxis (i.e. an acquired tolerance to treatment). This side-effect may be prevented by combination or rotation with non-corticosteroid products, including coal tar, dithranol, vitamin D_3 analogues or retinoids; such combinations may be synergistic.

Vitamin D_3 analogues

Currently, there are two vitamin D_3 analogues (calcipotriol and tacalcitol) on the market. They work by normalising the abnormal epidermal keratinocyte proliferation and differentiation in psoriasis, and may be anti-inflammatory. Topical vitamin D_3 analogues can clear psoriasis in 6–8 weeks and have the advantage of being clean, effective and relatively safe. They may cause irritation of uninvolved, perilesional skin. One tactic is to use either calcipotriol or tacalcitol once daily in the evening and a moderate-potency corticosteroid cream in the morning for 2–3 weeks. Vitamin D_3 analogues can be used cautiously on

the face and in flexural areas, and a scalp preparation of calcipotriol is also available. Extensive use of these compounds is limited by the potential for hypercalcaemia, thus it is recommended that calcipotriol use be restricted to 100 mg/week and tacalcitol restricted to 35 mg/week.

Topical retinoids

Retinoids probably act in psoriasis by directly normalising epidermal keratinocyte proliferation and differentiation. Recently, a topical third-generation acetylated retinoid called tazarotene has been shown to be effective in the treatment of psoriasis. Tazarotene is applied once daily in a gel formulation. The use of topical retinoids, such as tazarotene, may be limited by significant irritation of uninvolved skin. As a consequence, tazarotene is often avoided in highly pruritic psoriasis. As for vitamin D_3 analogues, their combination with tazarotene gel once daily (evening) and moderate-potency corticosteroid cream (morning) may enhance efficacy and reduce irritancy.

Site-specific first-line therapy

Scalp

The scalp is the anatomical site most commonly affected by psoriasis and paradoxically often the most difficult to treat successfully. Scalp psoriasis is often pruritic, and frequent scratching can lead to Köbnerisation (the appearance of psoriasis in sites of skin trauma) and worsening of the condition. Scalp treatments can be messy and greasy, and patients need to be advised regarding the correct use of treatments and their likely success. Otherwise, disappointment and a lack of confidence can affect compliance. There are a variety of treatments.

A tar preparation combined with a tar-containing or anti-fungal shampoo is the first-line therapy for scalp psoriasis. After washing the hair and towelling damp-dry, an ointment preparation, such as ung cocois co, is applied to the involved areas of the scalp and left overnight under plastic shower cap occlusion. The shower cap serves a dual purpose to allow penetration of the tar preparation into the plaques and to protect the bed linen. In the morning, the tar preparation is washed out with shampoo. This procedure, although messy, is usually effective and may be enhanced by the use of a corticosteroid or calcipotriol scalp solution in the morning after washing the hair. Dithranol or a mid-potency topical corticosteroid is recommended for the treatment of psoriasis at the hairline.

Flexural areas

The flexural form of psoriasis affects the axillae, sub-mammary skin, perineum and umbilicus, and is atypical in that friction and humidity in the skinfolds remove the scale, which may lead to diagnostic confusion. Flexural psoriasis is often very irritating, especially when sweating occurs. It may be difficult to control with topical therapy, the mainstay of which is mild-potency topical corticosteroids. A topical vitamin D_3 analogue or a mild tar preparation, if tolerated, can be tried in resistant cases.

Nails

Psoriasis affects the nails in up to 50% of patients, and more so if there is concomitant psoriatic arthritis or palmoplantar pustular psoriasis. If the nail is affected, it can be a useful sign when the diagnosis of psoriasis is in doubt. The most common nail signs are pitting, oil spots, onycholysis and subungal hyperkeratosis. Confusion with onychomycosis (dermatophyte nail infection) may occur. Nail clippings taken for microscopy and fungal culture should reveal or discount the presence of active dermatophyte infection, although it should be borne in mind that psoriasis and onychomycosis may co-exist. Topical treatment of nail psoriasis is difficult and largely ineffective. As a consequence, systemic treatment is almost always necessary to achieve significant improvement. However, topical treatments worth trying are either vitamin D_3 analogues or potent corticosteroids under occlusion for a week.

Second-line therapy

Second-line therapy for psoriasis is predominantly hospital based and dermatologist supervised. It is usually reserved for patients with severe, extensive disease unresponsive to topical therapy, those with erythroderma or pustular psoriasis, and patients with severe psychological distress resulting from their disease. The mainstays of such second-line treatment are inpatient or day-treatment centre therapy, phototherapy and systemic drugs. As for first-line therapy, the goal of treatment is to reduce the extent or severity of psoriasis to a level that allows the patient to carry out their daily activities in an unhindered fashion. Even systemic therapies are not curative.

Inpatient therapy

The main therapeutic regimens of inpatient or day-treatment centre management are the Goeckerman and Ingram regimens. The Goeckerman regimen involves the combination of coal tar and UVB phototherapy, whereas

Ingram therapy is the combination of dithranol and UVB phototherapy. Such treatments are often supplemented with other topical agents, such as corticosteroids and Vitamin D_3 analogues. Patients using dithranol or coal tar treatments are often immensely benefited by the simple fact that the nurses, rather than they themselves, are applying the treatments.

A dedicated dermatology inpatient unit, staffed by dermatology specialist nurses, is critical to the successful management of inpatients. Designated dermatology beds on a general medical ward with non-dermatology-trained staff is a far from ideal situation. Inpatient or day-treatment centre therapy can usually significantly improve psoriasis in 3 weeks.

Phototherapy

Phototherapy has been used for the treatment of psoriasis for 70 years, since Goeckerman pioneered the use of UVB (290–320 nm) as part of his tar regimen. Since then, monotherapy with UVB has played an important role in the management of psoriasis. UVB therapy is most often given on an outpatient basis, and the usual treatment regimen is three times weekly. The main side-effects are burning and potential carcinogenicity. Although animal studies suggest that UVB is carcinogenic, there is little evidence that the doses of UVB used to clear psoriasis can cause skin cancers. UVB-induced erythema is predominantly caused by the wavelengths 295–300 nm. Recent studies have shown, however, that the therapeutic wavelengths are in the region of 311–313 nm. This finding has led to the development of the TL-01 lamp, which emits a narrow spectrum of UV with a peak at 311 nm, the so-called 'narrowband' UVB.

Photochemotherapy (PUVA)

Photochemotherapy combines a photosensitising medication (psoralen) with long-wavelength (320–400 nm) ultraviolet A (UVA) light and is known as PUVA. UVA has a minimal acute biological effect when used in isolation but, when combined with psoralens, is used in the treatment of many dermatoses, especially psoriasis. Patients take psoralen tablets (8-methoxypsoralen [8-MOP]) 2 hours before exposure to UVA. PUVA can cause burning and an unpleasant pruritus called PUVA itch, and 8-MOP can cause significant nausea in a number of patients. Animal studies have suggested that PUVA therapy may cause cataracts. Although this effect has not been shown in humans, patients are advised to wear UVA protective glasses for 12 hours after PUVA therapy. Topical psoralen use, in the form of bathing in a dilute aqueous solution of psoralen prior to UVA exposure ('bath PUVA'), is also effective but is more expensive.

Long-term PUVA causes photoageing and non-melanoma skin cancers, especially cutaneous squamous cell carcinoma. The development of squamous cell carcinoma is related to the lifetime cumulative dose of PUVA received. A recent 20-year follow-up study suggested that ultra-high-dose PUVA was associated with the development of melanoma, although this study has been criticised. Modern PUVA regimens consist of twice weekly aggressive treatments in an attempt to clear psoriasis with the minimal number of PUVA exposures. Maintenance treatments are now avoided, except in exceptional circumstances. Small PUVA lamps can be used for treating psoriasis of the hands and feet.

Methotrexate

Methotrexate has been used in the treatment of severe psoriasis since the 1960s. It is given as a once weekly dose and has been reported to be effective in treating all forms of psoriasis. Its use is limited by potential side-effects. Methotrexate can cause marrow toxicity and hepatic fibrosis. The risk of hepatic fibrosis is increased in patients with a history of heavy alcohol intake, and patients are advised to abstain from alcohol while taking the drug. The hepatotoxicity of methotrexate is of concern because hepatic fibrosis can occur despite normal results on conventional liver function tests. This factor has led to recommendations that patients have a liver biopsy after every cumulative 1.5 g of the drug. Recently, it has been shown that serum levels of the aminoterminal peptide of type III procollagen, a marker of fibrosis, correlates with liver histology in patients with psoriasis who are taking methotrexate. This finding has led to reductions in the need for liver biopsy in centres that monitor this marker.

Cyclosporin

Cyclosporin was the first of the new immuno-modulatory drugs used to prevent transplant rejection and then used in the treatment of psoriasis based on its known suppressive effects on T lympho-cyte function. It inhibits T lympho-cyte activation, as indicated by a reduction in IL-2 production.

Low-dose cyclosporin (2.5–5.0 mg/kg/day) is preferred. Guidelines suggest that, prior to initiating treatment, the patient should be normotensive, with normal renal and hepatic function. For short-course, intermittent cyclosporin treatment, renal function can be adequately measured using serum creatinine, as long as an accurate

mean of three pre-treatment baseline readings is available.

Common side-effects of cyclosporin include paraesthesiae (e.g. burning sensation in the fingers), hypertrichosis, malaise and gingival hypertrophy. The main risks of prolonged treatment are hypertension and nephrotoxicity, indicated by a 30% or greater rise in serum creatinine above baseline. Thus, treatment courses should be limited to no more than 3–4 months at one time. Further treatment courses are allowable as long as major side-effects have not occurred. Cyclosporin should not be used in combination with phototherapy or photochemotherapy because of an increased risk of developing skin cancer.

Systemic retinoids

Retinoids have an anti-proliferative differentiating effect on epidermal keratinocytes. Although isotretinoin is weakly effective, the only systemic retinoid available for the treatment of psoriasis is the acid metabolite of etretinate, acitretin, which is a third-generation polyaromatic retinoid. Acitretin probably has a place in the armamentarium. Its drawbacks are symptomatic side-effects and perceived lower response rates compared with other systemic therapies, but its relative safety in terms of carcinogenicity or organ toxicity justifies its continued use in the management of severe psoriasis. Prior to treatment, liver function and fasting lipid levels should be measured because acitretin is occasionally heptatotoxic and may increase serum levels of cholesterol and triglycerides. The major side-effect of acitretin is its undoubted teratogenicity, so ideally it should not be given to women with child-bearing potential, even if using contraception, because the drug's half-life in the body is substantial. Women should be advised not to become pregnant for a least 24 months after stopping treatment with acitretin. Some patients on long-term treatment have developed diffuse interstitial skeletal hyperostosis syndrome. Most if not all patients taking acitretin complain of cheilitis and xerosis and, more rarely, alopecia and sticky, fragile skin. Acitretin is frequently combined with PUVA treatment.

Generalised pustular and palmoplantar pustular psoriasis are particularly responsive to acitretin, which is sometimes the only treatment that will help these forms of psoriasis.

Hydroxyurea

The anti-metabolite hydroxyurea may be useful in patients who are intolerant of or have developed side-effects from other systemic modalities. It is given at a dose of 0.5–1.5 g daily, and its main side-effect is marrow suppression, which has led to concerns regarding its safety and has reduced its use for treating severe psoriasis.

Fumarates

Esters of fumaric acid are not licensed for use in the UK; however, they are extensively used as a second-line therapy for psoriasis in Germany and The Netherlands.

Azathioprine

Azathioprine is generally ineffective in treating psoriasis, although the occasional patient benefits from its use. Its main side-effects are marrow suppression and hepatotoxicity.

Sulphasalazine

Although rarely used for the treatment of psoriasis in the UK, there is support for the use of sulphasalazine in the USA, particularly with its known efficacy in inflammatory bowel disease and rheumatoid arthritis. Sulphasalazine is generally given at a dose of 3–4 g daily, although about 25% of patients are unable to tolerate it.

Combination therapies

In an effort to reduce the potential toxicities of individual systemic agents in the treatment of severe psoriasis, there have been reports of the use of combinations of low doses of systemic agents. These include combining acitretin and PUVA (RePUVA) and combining methotrexate and PUVA. The combination of PUVA and cyclosporin is not recommended because of an additive increased risk of cutaneous cancers. There have been reports of combination treatment with methotrexate and cyclosporin in patients who have concomitant psoriasis and psoriatic arthropathy. Cyclosporin has also been used in combination with hydroxyurea for resistant psoriasis.

Costs of psoriasis treatment

Some prescription items used for the treatment of psoriasis are also used to treat diseases other than psoriasis, therefore the actual drug costs to the NHS of psoriasis treatment are difficult to ascertain. For instance, topical corticosteroids are used for treating eczema, methotrexate is prescribed for rheumatoid arthritis and malignancy, and cyclosporin is used to prevent transplant rejection and to treat a variety of autoimmune conditions. In addition to drugs, the costs of phototherapy, day-treatment centre care and inpatient care also need to be factored in when calculating the financial burden of managing severe psoriasis.

Chapter 2
Methods

Research questions for the current review

The current systematic review was carried out in order to:

1. compare the effectiveness of currently available treatments (including pharmacological treatments and phototherapy) for severe psoriasis
2. identify, on the basis of a systematic review, those areas where further research should be undertaken.

The review was carried out using structured guidelines for systematic reviews (NHS Centre for Reviews and Dissemination, 1996). A range of sources was searched in order to identify trials of treatments for severe psoriasis. Abstracts of experimental studies were retrieved and screened for inclusion by two reviewers. Full papers were then retrieved, and the process was repeated to arrive at the final list. Data were extracted and presented in tabular form. The sources, inclusion criteria and assessment of study validity are described below.

A separate search was carried out to identify primary studies and reviews of economic evaluation of the treatment of severe psoriasis.

Development of citation database (sources)

There were three steps in the process of developing a citation database: definition of inclusion/exclusion criteria, identification of reports and information management.

Inclusion/exclusion criteria

A report was regarded as eligible if it fulfilled the following criteria.

- Allocation of the patients to the intervention was described as randomised (no precise description of the method of randomisation was required), double-blind or both, or if it was implied that the interventions were given at random or under double-blind conditions.
- The psoriasis was described as severe, widespread, extensive, recalcitrant, resistant to topical treatment or a combination of these.
- The report concerned the treatment of psoriasis (i.e. induction of remission or maintenance of remission).

Reports were excluded if they concerned exclusively palmoplantar pustular psoriasis, guttate psoriasis or psoriatic arthritis.

Identification of reports

A broad electronic search strategy was used to ensure that a thorough examination of the literature could be carried out. The objective was to identify all the studies concerned with the treatment of severe psoriasis. Randomised controlled trials (RCTs) were then extracted from the database and used for the review. Relevant studies in any language were accepted.

Searches of MEDLINE (from 1966 through June 1999) and EMBASE (from 1980 through June 1999) were conducted using SilverPlatter® configuration (*Table 1*). The subject terms 'psoriasis', 'treatment' and 'psoriasis-drug-therapy' were used to search title, abstract and keyword sections. The additional terms 'study', 'trial*', 'random*' in the text, 'compar*' in the title or 'clinical-trial' in the subject heading were used to increase the specificity of the search. Subject terms, for example, 'cyclosporin* or ciclosporin' were then used to group trials according to intervention. Recent reviews of methotrexate treatment were used to identify methotrexate trials, because the original studies with this agent were done before 1966.

The search findings were checked against the Cochrane Register of Randomised Controlled Trials, using 'psoriasis' as a search term (*Table 1*). Author names identified from trials and key review papers were used to search the Science Citation Index. The European Dermato-Epidemiology Network (EDEN) trials register was checked. Attempts were made to locate studies that had not been identified by electronic searching. This process included looking at selected conference proceedings (e.g. Psoriasis From Gene to Clinic, London, UK, December 1996, and 7th

TABLE 1 *Search results*

	Number of records
Records identified by MEDLINE search	1553
Additional records identified by EMBASE search	1289*
Additional records identified by Cochrane search	10
Additional records identified by hand-searches, etc.	21
Total	**2873**

**1289 additional records were identified; 798 duplicates were also found*

International Psoriasis Symposium, Milan, Italy, September 1998).

Manufacturers were contacted to identify additional studies. Recent conference proceedings were hand-searched. Recent issues of key dermatology journals (*Journal of the American Academy of Dermatology*, *British Journal of Dermatology* and *Archives of Dermatology*) were hand-searched. As papers were retrieved, the references were checked to identify additional trials. Dermatologist colleagues were asked to review the lists of reports generated to identify missing reports.

Information management

The records identified by electronic searching were downloaded (Bibliolink v.1.1, Personal Bibliographic Software Inc., USA) and transferred to a reference management programme (Pro-Cite v.3.1, Research Information Systems, USA). When additional records were found, the details were entered manually into the database. The records were then sorted in both alphabetical and date order, and each abstract was checked on-screen for definite eligibility, probable eligibility or ineligibility. The records were coded within Pro-Cite for eligibility (including trial type and intervention) for easy retrieval (*Table 2*). A second reviewer screened the records, and then hard copies of all studies thought to be eligible were obtained and eligibility was confirmed.

Papers in the following languages (besides English) were identified: French, German, Spanish, Italian, Swedish, Polish, Czech, Turkish, Chinese, Japanese and Korean. The reviewers were able to read studies in French, German, Italian and Spanish. Help was sought for the studies reported in other languages.

Study validity, data extraction and synthesis

Trials were considered to be valid if they met the inclusion criteria and contained sufficient data for further analysis. Trials were excluded at this stage if they were duplicate publications or if the data presented were subsets of data reported elsewhere.

All potentially comparable input and outcome data were extracted and recorded in tables by using Minitab® software v.10.2, 1994 (Minitab Inc., USA). These tables formed the basis for our analysis and enabled us to establish clinically meaningful comparisons.

TABLE 2 *Breakdown of citations by treatment*

Treatment	Citations	Trials of all types	RCTs	RCTs included in review
Azathioprine	14	1	0	0
Cyclosporin	169	88	37	18
Fumarates	20	9	5	5
Hydroxyurea	6	4	1	1
Methotrexate	111	31	2	0
Phototherapy (including PUVA and UVB)	332	–	93	51
Retinoids	170	108	56	33
Sulphasalazine	10	5	1	1

Statistical analysis and outcome measures

The PASI[25] is frequently used to assess the outcome of psoriasis treatment, but it was not used for all the RCTs included in this overview. Furthermore, the authors who did use it presented the results in two different ways. Some presented average scores for study groups before and after the intervention, whereas others reported the average percentage decrease in PASI. Clearly, the first approach works best when the groups contain patients with disease of similar severity, and the second approach works well when there is a wider range of baseline disease severity. The results from these two different approaches cannot readily be interconverted using the information available in the published papers. Although the PASI initially appeared to be the most satisfactory outcome measure, its sole use for analysis would have resulted in the loss of too much information obtainable from other outcome measures.

An alternative approach in this situation is to find a way to dichotomise the results (i.e. turn them into a yes/no, alive/dead, cured/not cured format). Several authors had presented their results in this form already. In the context of psoriasis, results can be divided into cleared/not cleared or, more conservatively, successful/unsuccessful. The most widely used criterion was a decrease in PASI of at least 75% or a decrease to an absolute value of 8 or less. It was assumed that this criterion would correspond to the category of 'clear' or 'almost clear' used by other authors.

Several statistical methods exist to derive pooled estimates of effects from dichotomous data. The Mantel-Haenzsel method[26] or Peto method[26] can be used to calculate an odds ratio (OR) after a 2 × 2 table has been constructed for each trial in the overview (*Table 3*).

The OR for the trial is therefore:

$$\frac{a/c}{b/d} = \frac{ad}{bc}$$

The Mantel-Haenzsel pooled OR is calculated as:

$$\frac{\text{Sum } (\text{weight}_i \times \text{OR}_i)}{\text{Sum weight}_i}$$

where $\text{weight}_i = 1/\text{variance}_i$
and $\text{variance}_i = n_i / (b_i \times c_i)$

TABLE 3 *Arrangement of data for Mantel-Haenzsel and Peto methods*

	Treated	Not treated	Total
Diseased	*a*	*b*	*g*
Not diseased	*c*	*d*	*h*
Total	*e*	*f*	*n*

Difficulties arise with these methods when a value of zero appears in one of the cells, causing the OR to be either zero or infinity. Some statisticians recommend that 0.5 should be added to each cell in this situation, although this does not work well if the total sample size is small.[27]

An alternative approach is to use the difference in event rates (i.e. success or response) as the summary measure of effect. This approach has the advantage that the result – the average success rate (risk) difference (RD) – is more easily interpretable than an OR or rate ratio.

The proportion of patients in whom treatment is successful can be expressed as a value between 0 and 1 (corresponding to 0–100%). If p_1 is the proportion of successfully treated patients in the test group and p_2 is the proportion in the placebo (control) group, then the RD is $p_1 - p_2$. A positive value shows that the treatment is more efficacious than the control, and a value of zero shows that there is no difference between the two. If the 95% confidence interval (CI) around the RD includes the value of zero, then it cannot be assumed that there is a difference between the two treatments.

The average success RD is:

$$\text{RD}_s = \frac{\text{Sum } (\text{weight}_i \times \text{RD}_i)}{\text{Sum } (\text{weight}_i)}$$

where $\text{weight}_i = 1/\text{variance}_i$

RD_i = event RD for ith study

variance (v_i) of RD = $p_{i1}(1 - p_{i1})/n_{i1} + p_{i2}(1 - p_{i2})/n_{i2}$

where p_{i1} and p_{i2} are the proportions of individuals in the experimental and control groups, respectively, who have the condition (treatment success), and event RD = $(p_{i1} - p_{i2})$

Homogeneity is tested using the Q statistic:

$$Q = \text{Sum}\ [\text{weight}_i\ (\text{RD}_s - \text{RD}_i)^2]$$

Q is referred to the chi-square distribution, with degrees of freedom equal to the number of studies minus one.

The 95% CI for the pooled estimate is given by:

$$\text{mean}_s \pm [1.96\ \sqrt{(\text{variance}_s)}]$$

where $\text{variance}_s = 1/\text{sum weight}_i$

For this review, success RDs were displayed graphically by means of forest plots. Where homogeneity across trials could be demonstrated, pooled RDs were calculated.

Chapter 3
Cyclosporin

Summary

In total, 18 RCTs were included in this review of cyclosporin therapy for psoriasis: 13 reports concerned the induction of remission of psoriasis, and five concerned the maintenance of remission.

The main outcome measure was treatment success measured by a specified decrease in either PASI or the extent of body surface area involved or by a global improvement scale. Dichotomous data for effectiveness were analysed using RDs. It was not always possible to pool data because of marked heterogeneity. Identifiable sources of heterogeneity included the initial severity of disease, cyclosporin dose, success criterion, duration of treatment and formulation of cyclosporin. Compliance may represent a further source of heterogeneity.

Cyclosporin doses in the range of 2.5–5.0 mg/kg/day were associated with optimal response RDs. Doses of 5.0 mg/kg/day were associated with increased response rates compared with doses of 2.5 mg/kg/day. However, any advantage in efficacy achieved using doses greater than 5.0 mg/kg/day may be offset by an increase in dose-related side-effects, particularly a rise in creatinine.

Maintenance treatment required a dose of 3.0–3.5 mg/kg/day and may be more effective at preventing relapse if given continuously. However, the risk of side-effects is most likely increased if treatment is given in a continuous fashion long-term as opposed to intermittently.

Low-dose cyclosporin appeared to be more effective than etretinate.

The addition of calcipotriol had an additive effect on response rate.

Background

Cyclosporin is an undecapeptide derived from the soil fungus *Tolypocladium inflatum gams*, whose unique T cell immunosuppressive properties were first realised in 1975.[28] Incorporation of the drug into transplant rejection prophylaxis programmes was rapid, and its introduction undoubtedly improved the prognosis and quality of life of many transplant patients. The mechanism of action of cyclosporin is dependent on its binding to a cytosolic immunophilin called cyclophilin. The resultant cyclosporin–cyclophilin complex binds to a cytosolic enzyme, calcineurin phosphatase, within T cells (and other cells). This binding process inhibits the ability of calcineurin phosphatase to dephosphorylate the cytosolic component of the nuclear transcription factor of activated T cells (NFAT), which enables its translocation into the nucleus. Ordinarily, after its translocation into the nucleus, NFAT would regulate transcription of a variety of T cell cytokines, most importantly, IL-2, the key determinant of T cell activation.[29] Cyclosporin thus blocks the intracellular components of T cell activation.

The first report of the beneficial affects of cyclosporin in the treatment of psoriasis came in 1979. In a letter to the *New England Journal of Medicine*, two Swiss rheumatologists reported that, during a study of the utility of high-dose cyclosporin for the treatment of arthritis, they treated patients with psoriatic arthritis.[30] The patients with concomitant psoriasis were rapidly cleared of their skin lesions. A number of clinical studies quickly followed, as a result of which cyclosporin was granted a UK licence in 1992 for the treatment of "patients with severe psoriasis in whom conventional therapy is ineffective or inappropriate".[31] In the USA, cyclosporin is licensed for the treatment of severe, recalcitrant plaque psoriasis in adults who are immunocompetent.

Despite the undoubted efficacy of cyclosporin in treating psoriasis, its use has been restricted because of concerns about dose-dependent renal impairment and hypertension as well as because of its high acquisition cost.

Clinical studies are now concentrated on strategies to reduce unwanted side-effects. These studies involve intermittent, short courses of cyclosporin.

Search results

In total, 169 citations were identified for cyclosporin. Of these, 88 were clinical reports or studies of cyclosporin, including RCTs, controlled trials (non-randomised), retrospective studies, case reports and small series. Titles and abstracts were reviewed by two people independently to identify RCTs. Thirty-seven citations appeared to be reports of RCTs; of these, 34 citations concerned the use of systemic cyclosporin, and five concerned the use of topical cyclosporin. All these reports were retrieved and read.

Nineteen studies were excluded from the final review (see appendix 1). Two of these reports were duplicate publications, two were subsets of a multicentre study, five were non-randomised studies, and five were reports of topical or intralesional cyclosporin. Two studies were excluded because they contained insufficient data for analysis, and one was excluded because it was concerned with mild psoriasis. One study was excluded because the data were contained in a later publication. One further study was excluded because no English translation of the Japanese original was available. Eighteen trials were thus available for inclusion in this review.

Characteristics of included studies

These 18 trials comprised 13 trials of treatment to induce remission of psoriasis and five trials of treatment to maintain remission.[17,32–48] The characteristics of the trials are shown in *Tables 4* and *5*.

RCTs of cyclosporin to induce remission of psoriasis

In order to determine whether or not the data from the separate trials could reasonably be pooled statistically, the reports were examined to determine the degree of similarity between them. The trials differed considerably with respect to four main variables, namely, the initial severity of disease, cyclosporin dose, success criterion and duration of treatment. It is likely that these differences would give rise to marked variation in success rates. However, other factors, such as interacting drugs or variable compliance with the dose regimens, cannot be discounted.

The pre-treatment severity of disease was described in several ways. In seven of the trials, a threshold level of the PASI was used, usually in conjunction with other secondary criteria, such as the percentage of body surface area affected, failure to respond to at least one other systemic treatment or prolonged duration of disease. Two trials[17,32] expressed disease severity as the percentage of body surface area affected and used threshold values of 20% and 25%. The remainder of the trials simply described the disease as 'moderate to severe' or 'severe'. The threshold levels for the PASI ranged from 8 to 20.

In ten of the studies, the criterion for success was expressed as a change in the PASI; the remaining two trials used the descriptions of 'clear', 'almost clear' or 'markedly improved'. Seven trials used a 75% decrease in PASI or a final PASI score of 8 or less as the criterion for success. Guenther and Wexler[33] used a decrease in PASI of 50% as the criterion for success and reported a successful outcome in 11 of 12 patients (92%). At the opposite end of the scale, Grossman and colleagues[34] used a 90% decrease in PASI as the success criterion and reported a successful outcome in four of 34 (12%) patients. Meffert and co-workers[35] used a success criterion of a 75% decrease in PASI but included patients with PASI as low as 8. These authors reported successful outcomes in four of 41 (10%) and 12 of 44 (27%) patients receiving daily doses of 1.25 and 2.5 mg/kg, respectively.

The dose of cyclosporin ranged from 1.25 to 14 mg/kg/day. Two patient series received doses of 1.25 mg/kg/day and achieved success rates of 10% and 18%. Seven patient series received doses of 2.5–3.0 mg/kg/day and achieved success rates of 28–92%. Six patient series received doses of 5.0 or 5.5 mg/kg/day and achieved successful outcomes in 50–97% of patients. In one study that compared a very high dose of cyclosporin (14 mg/kg/day) with placebo, improvement was rapid but associated with increased serum creatinine in four of the 11 patients receiving cyclosporin. Interestingly, seven of the 11 patients receiving cyclosporin and seven of the ten patients receiving placebo had an increase in diastolic blood pressure.

The duration of treatment in the trials ranged from 4 to 12 weeks, which must contribute to the variability of the results reported. Trials that have reported cumulative success rates have shown that the response curve does not level out until after 12 or 16 weeks of treatment, which suggests that trials that end earlier are likely to show greater variability in outcomes than do trials of longer duration.

TABLE 4 *Design of trials of cyclosporin used to induce remission of psoriasis*

Trial	Intervention	Comparator	Design and duration	*n:n* (CSA: comparator)	Inclusion criterion (disease severity)	Success criterion
Cyclosporin vs placebo						
Ellis, 1986[32]	CSA, 14 mg/kg	Placebo	DB, parallel group, 4 weeks	11:10	BSA affected > 20%	Clear or almost clear
Ellis, 1991[17]	CSA, 3.0 mg/kg CSA, 5.0 mg/kg CSA, 7.5 mg/kg	Placebo	DB, parallel group, 8 weeks	25:25 20:25 15:25	BSA affected > 25%	Clear or almost clear
Engst, 1989[47]	CSA, 5 mg/kg	Placebo	DB, parallel group, 4 weeks	6:6	PASI > 20	75% decrease in PASI, or PASI < 8
Guenther, 1991[33]	CSA, 2.5 mg/kg	Placebo	DB, parallel group, 10 weeks	12:11	PASI > 12	50% decrease in PASI
Meffert, 1997[35]	CSA, 1.25 mg/kg CSA, 2.50 mg/kg	Placebo	DB, parallel group, 10 weeks	41:43 44:43	PASI, 8–25	75% decrease in PASI
van Joost, 1988[48]	CSA, 5.5 mg/kg	Placebo	DB, parallel group, 4 weeks	10:10	Not reported	75% decrease in PASI, or PASI < 8
Cyclosporin vs etretinate						
Finzi, 1993[45]	CSA, 5 mg/kg	Etretinate, 0.75 mg/kg	DB, parallel group, 12 weeks	36:40	PASI > 15	75% decrease in PASI, or PASI < 8
Mahrle, 1995[46]	CSA, 2.5 mg/kg	Etretinate, 0.5 mg/kg	SB, parallel group, 10 weeks	140:70	"Moderate–severe"	70% decrease in PASI
Cyclosporin in different doses						
Christophers, 1992[41]	CSA, 1.25 mg/kg CSA, 2.50 mg/kg	CSA, 2.50 mg/kg CSA, 5.00 mg/kg	NB, parallel group, 12 weeks	36:121 121:60	PASI > 15	75% decrease in PASI
Laburte, 1994[42]	CSA, 2.5 mg/kg	CSA, 5.0 mg/kg	NB, parallel group, 12 weeks	119:132	Not reported	75% decrease in PASI, or PASI < 8
Cyclosporin and calcipotriol						
Grossman, 1994[34]	CSA, 2 mg/kg, + calcipotriol	CSA, 2 mg/kg, + placebo ointment	DB, parallel group, 6 weeks	35:34	PASI > 20	90% decrease in PASI
Cyclosporin: comparisons of formulations						
Elder, 1995[44]	CSA (Neoral), 300 mg	CSA (Sandimmun), 300 mg	DB, crossover (modified), 12 weeks	18:19	PASI ≥ 12	Marked improvement or clearance
Koo, 1998[43]	CSA (Neoral), 2.5 mg/kg	CSA (Sandimmun), 2.5 mg/kg	DB, parallel group, 12 weeks	152:156	PASI > 15	75% decrease in PASI

CSA, cyclosporin A; DB, double-blind; SB, single-blind; NB, not blinded; BSA, body surface area

TABLE 5 *Design of trials of cyclosporin used to maintain remission of psoriasis*

Trial	Intervention	Comparator	Design and duration	*n:n* (CSA: comparator)	Success criterion
Cyclosporin vs placebo					
Ellis, 1995[36]	CSA, 1.5 mg/kg CSA, 3.0 mg/kg	Placebo	DB, parallel group, 16 weeks	19:20 21:20	Increase of no more than 2 points on a 7-point scale
Shupack, 1997[37]	CSA, 1.5 mg/kg CSA, 3.0 mg/kg	Placebo	DB, parallel group, 24 weeks	7:49 86:49	Increase in BSA affected to no more than 50% of baseline score
Cyclosporin: comparisons of treatment schedules					
Ozawa, 1999[38]	CSA (continuous), 5 mg/kg	CSA (intermittent), 5 mg/kg	NB, parallel group, 36 months*	17:20	Increase in PASI to no more than 50% of baseline score
Ho, 1999[40]	CSA, 2.5–5.0 mg/kg, abruptly discontinued	CSA, 2.5–5.0 mg/kg, gradually discontinued	NB, parallel group, 12 months	192:173	Increase to no more than 75% of pre-treatment disease extent
Cyclosporin: comparisons of formulations					
Zachariae, 1998[39]	CSA (Sandimmun), 3 mg/kg	CSA (Neoral), 3 mg/kg	NB, parallel group, 24 weeks	28:30	Increase of no more than 2 points on a global scale, or increase in PASI score to no more than 8

**Minimum of 36 months of treatment; mean treatment duration, 46.0 ± 3.4 months*

RCTs of cyclosporin to maintain remission of psoriasis

Table 5 shows the design of trials using cyclosporin to maintain the remission of psoriasis. Two trials[36,37] compared two doses of cyclosporin with placebo. Ozawa and co-workers[38] compared intermittent and continuous dosing, and Zachariae and colleagues[39] compared two formulations of cyclosporin. Ho and co-workers[40] compared the effects of abrupt and gradual discontinuation of cyclosporin. The success criteria were slightly different for each study. Ellis and colleagues[36] used an increase of no more than two points on a 7-point global assessment scale. Ozawa and co-workers[38] used an increase to no more than 50% of the pre-study baseline PASI score, Shupack and colleagues[37] employed an increase to no more than 50% of the pre-study baseline body surface area affected, and Zachariae and colleagues[39] described an increase of up to 8 in the PASI score or an increase of up to 2 points in a global score (the total number of points on the latter scale was not reported). Ho and co-workers[40] defined relapse as the recurrence of psoriasis affecting 75% or more of the pre-treatment disease extent. The doses of cyclosporin employed to maintain remission also varied between 1.5 and 5 mg/kg/day.

Results

Induction of remission

RCTs of cyclosporin versus placebo

Table 6 and *Figure 1* show the success RDs for the trials that compared cyclosporin with placebo. The large variations in success RDs (from 0.05 to 0.83) suggest that this data set is heterogeneous, which is confirmed by statistical analysis ($Q = 87.24$; degrees of freedom, 8; fixed effects model). The major factors that contributed to the observed heterogeneity appear to be the marked differences in doses, treatment duration and success criteria, as well as the variation in baseline disease severity, as described above. The only study in which the CIs appeared to lie outside the general pattern used a success criterion of a reduction in PASI of only 50%.[33]

RCTs comparing different doses and formulations of cyclosporin

Two studies compared different doses of cyclosporin in non-blinded studies over a period of 12 weeks (*Table 7*).[41,42] Christophers and co-workers[41] compared three dose levels (1.25, 2.50 and 5.00 mg/kg/day), and Laburte and co-workers[42] compared two dose levels (2.5 and 5.0 mg/kg/day). *Table 7* and *Figure 2* show the success RDs between the regimens of 5.0 and 2.5 mg/kg/day.

Koo[43] compared the conventional oil-based cyclosporin formulation (Sandimmun®, Novartis Pharma, Switzerland) with the microemulsion pre-concentrate formulation (Neoral®, Novartis Pharma, Switzerland) in a 12-week study. As shown in *Table 8,* success rates were similar in the two groups (0.78 and 0.80, respectively). Elder and colleagues[44] also com-pared Sandimmun with Neoral in a 12-week, crossover study. They reported no overall differences in efficacy between the two formulations (*Table 8*), although Neoral appeared to have greater efficacy at selected time-points. The microemulsion pre-concentrate was introduced in 1995 in order to improve the reliability of gastrointestinal absorption.[44]

TABLE 6 *Treatment success RDs: cyclosporin (all doses) compared with placebo for induction of remission (trials ranked by dose)*

Trial	CSA dose (mg/kg/day)	*n:n* (CSA:placebo)	Weight	RD	(95% CI)
Meffert, 1997[35]	1.25	41:43	303.05	0.05	(–0.06 to 0.16)
Meffert, 1997[35]	2.5	44:43	179.08	0.22	(0.07 to 0.37)
Guenther, 1991[33]	2.5	12:11	73.64	0.83	(0.60 to 1.06)
Ellis, 1991[17]	3	25:25	108.51	0.36	(0.17 to 0.55)
Engst, 1989[47]	5	6:6	15.34	0.33	(–0.17 to 0.83)
Ellis, 1991[17]	5	20:25	87.91	0.65	(0.44 to 0.86)
Van Joost, 1988[48]	5.5	10:10	47.62	0.7	(0.42 to 0.98)
Ellis, 1991[17]	7.5	15:25	93.75	0.8	(0.60 to 1.00)
Ellis, 1986[32]	14	11:10	55.81	0.73	(0.47 to 0.99)
Pooled rate (fixed effects), $Q = 87.24$				0.38	(0.32 to 0.44)

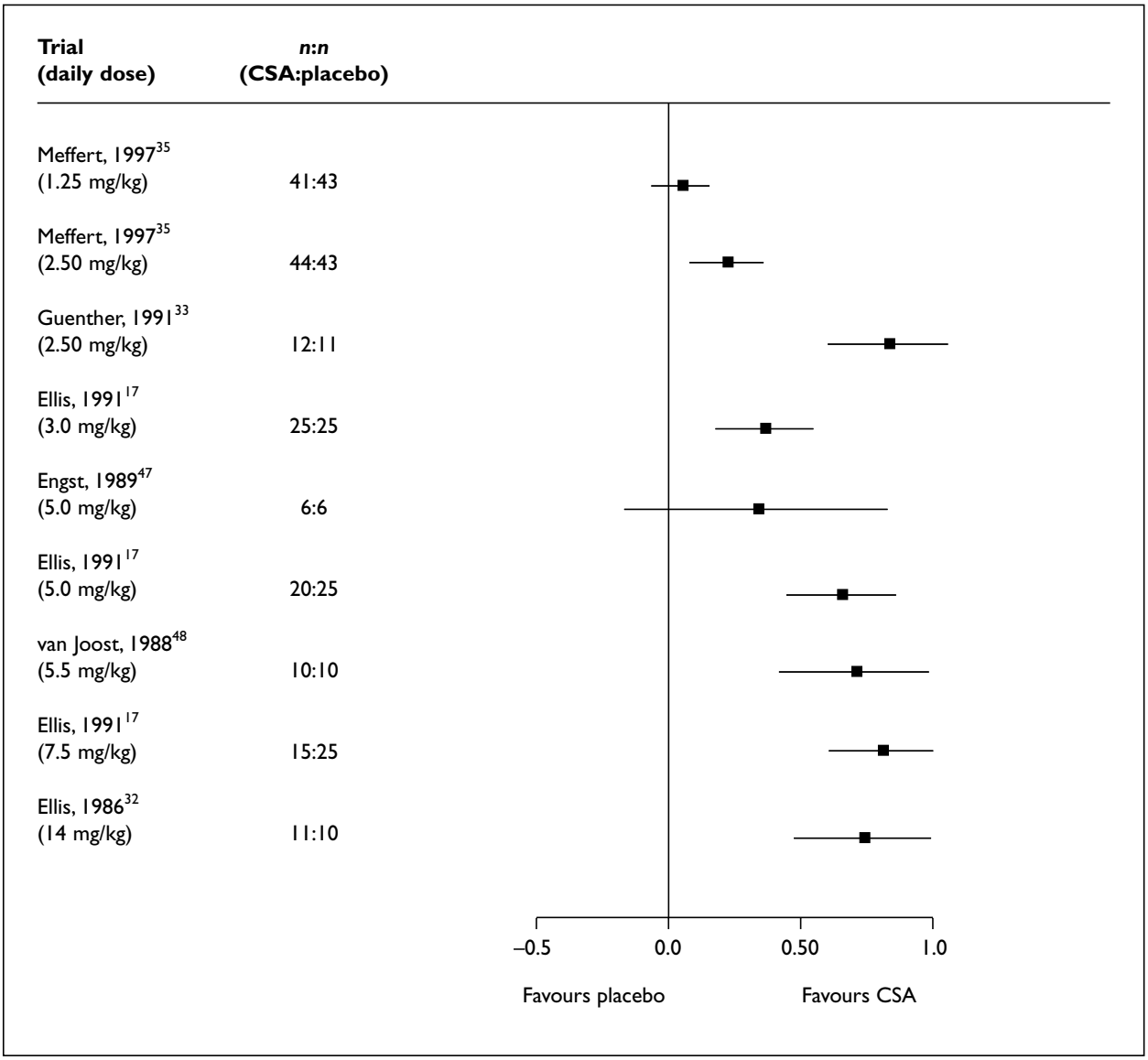

FIGURE 1 *Cyclosporin versus placebo: RDs (95% CI)*

TABLE 7 *Treatment success RDs: different doses of cyclosporin*

Trial	Intervention	Comparator	Success criterion	Response rate (5.0 mg/kg:2.5 mg/kg)	RD (95% CI)
Christophers, 1992[41]	CSA, 5.0 mg/kg	CSA, 2.5 mg/kg	75% decrease in PASI	0.68:0.49	0.19 (0.04 to 0.34)
Laburte, 1994[42]	CSA, 5.0 mg/kg	CSA, 2.5 mg/kg	75% decrease in PASI, or PASI < 8	0.89:0.48	0.41 (0.31 to 0.51)

RCTs comparing cyclosporin with etretinate

Table 9 and *Figure 3* show success RDs for the two trials that compared cyclosporin with etretinate.[45,46] The trials produced very different results in the cyclosporin-treated groups (success rates of 0.97 and 0.62, respectively), and the difference in cyclosporin doses should be noted.

Other cyclosporin RCTs

Grossman and colleagues[34] compared low-dose cyclosporin alone or combined with calcipotriol ointment. The trial had a very strict success criterion (> 90% reduction in PASI) yet demonstrated a high success rate for low-dose cyclosporin combined with topical calcipotriol.

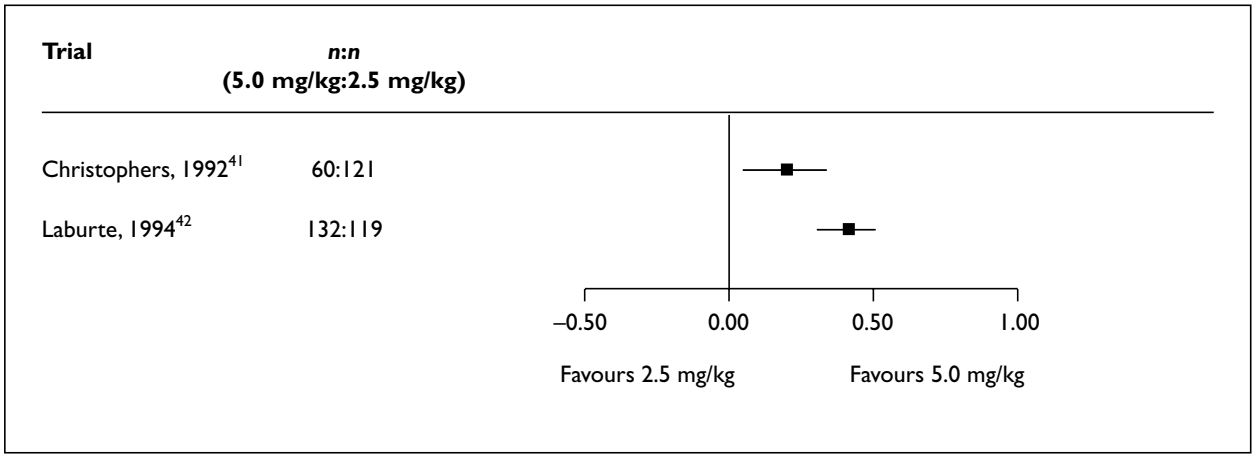

FIGURE 2 *Cyclosporin, daily dose of 5.0 versus 2.5 mg/kg: RDs (95% CI)*

TABLE 8 *Treatment success RDs: different formulations of cyclosporin*

Trial	Intervention	Comparator	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Elder, 1995[44]	CSA (Neoral), 300 mg, for 8 weeks Then CSA (Sandimmun), 300 mg, for 4 weeks	CSA (Sandimmun), 300 mg, for 8 weeks Then CSA (Neoral), 300 mg, for 4 weeks	Marked improvement or clearance	0.88:0.82	0.06 (–0.17 to 0.28)
Koo, 1998[43]	CSA (Neoral), 2.5 mg/kg	CSA (Sandimmun), 2.5 mg/kg	75% decrease in PASI	0.80:0.78	0.02 (–0.07 to 0.11)

TABLE 9 *Treatment success RDs: cyclosporin (any dose) versus etretinate (any dose)*

Trial	Dose (mg/kg/day)		*n:n* (CSA:etretinate)	Response rate (CSA: etretinate)	RD (95% CI)
	CSA	Etretinate			
Finzi, 1993[45]	5.0	0.75	36:40	0.97:0.73	0.24 (0.09 to 0.39)
Mahrle, 1995[46]	2.5	0.5	140:70	0.62:0.16	0.46 (0.34 to 0.58)

Maintenance of remission

RCTs comparing cyclosporin with placebo for maintaining remission

Table 10 and *Figure 4* show the success RDs for the two studies that compared maintenance cyclosporin treatment with placebo. Presented as the proportion of patients still in remission at the end of the trial, the results demonstrate that the success rates for active treatment ranged from 0.21 to 0.58. In the placebo-treated groups, the proportions of patients remaining in remission at the conclusion of the trials were 0.05 and 0.16.[36,37]

The results of these two studies suggest that cyclosporin is superior to placebo in maintaining remission if given at a dose of at least 3.0 mg/kg, but not at a dose of 1.5 mg/kg. The randomisation schedule of 1:7 (placebo:cyclosporin) used in the Shupack study[37] is unusual; however, it is understandably used with a view to attracting patients into such a long-term study.

RCT comparing two formulations of cyclosporin (Sandimmun versus Neoral)

The one study that compared two different formulations of cyclosporin (Sandimmun and

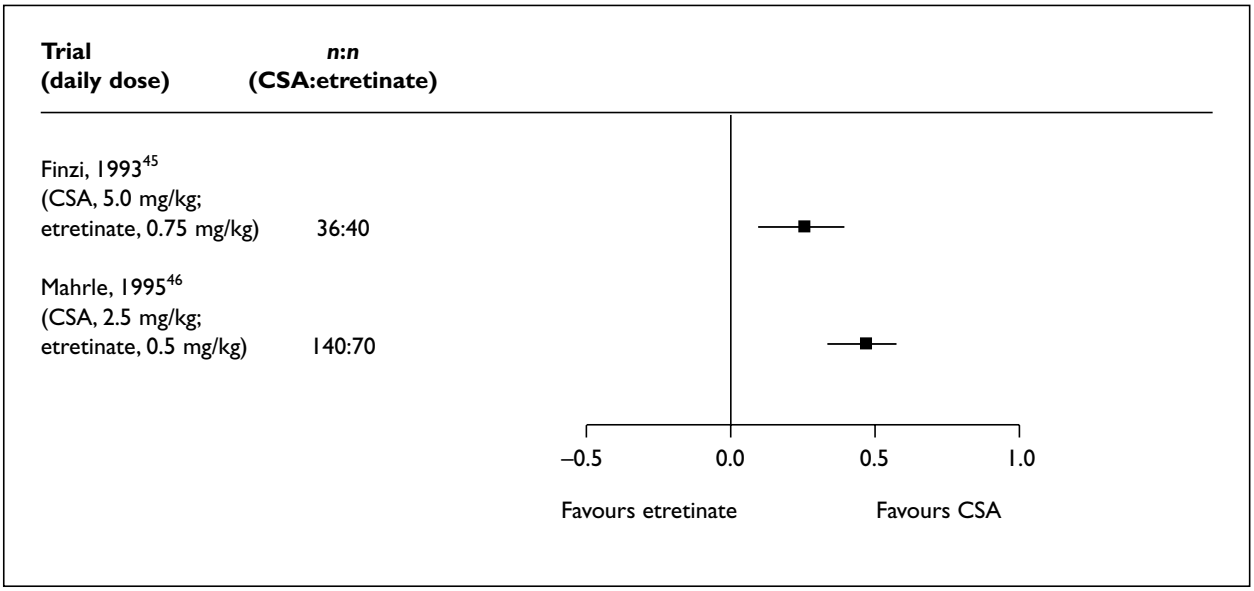

FIGURE 3 *Cyclosporin versus etretinate: RDs (95% CI)*

TABLE 10 *Maintenance treatment success RDs*

Trial	Intervention	Comparator	Success criterion	Response rate (CSA:comparator)
Cyclosporin vs placebo				
Ellis, 1995[36]	CSA, 1.5 mg/kg CSA, 3.0 mg/kg	Placebo	Increase of no more than 2 points on a 7-point scale	0.21:0.05 0.57:0.05
Shupack, 1997[37]	CSA, 1.5 mg/kg CSA, 3.0 mg/kg	Placebo	Increase in BSA affected to no more than 50% of baseline score	0.00:0.16 0.58:0.16
Cyclosporin: comparisons of treatment schedules				
Ozawa, 1999[38]	CSA (continuous), 5 mg/kg	CSA (intermittent), 5 mg/kg	Increase in PASI to no more than 50% of baseline score	Data unsuitable for this type of analysis
Ho, 1999[40]	CSA, 2.5–5.0 mg/kg, abruptly discontinued	CSA, 2.5–5 mg/kg, dose gradually discontinued	Increase to no more than 75% of pre-treatment disease extent	Data unsuitable for this type of analysis
Cyclosporin: Sandimmun vs Neoral				**(Neoral:Sandimmun)**
Zachariae, 1998[39]	CSA (Neoral), 3 mg/kg	CSA (Sandimmun), 3 mg/kg	Increase of no more than 2 points on a global scale, or increase in PASI score to no more than 8	0.60:0.68

Neoral) for maintenance treatment showed both were equally effective over a 24-week period (*Tables 5* and *10*).[39]

RCT comparing continuous versus intermittent dosing of cyclosporin

Ozawa and colleagues[38] compared continuously dosed cyclosporin with intermittently dosed cyclosporin for maintenance treatment (*Table 5*). They analysed the results from patients who had completed a minimum of 36 months of treatment. The periods of relapse were longer in the intermittently treated group, and the periods of remission were shorter in this group.

Analysis of the results of Ozawa and colleagues shows that an average daily dose (± standard error of the mean [SEM]) of 3.20 ± 0.21 mg/kg, delivered as continuous therapy, kept patients in remission for 69% of the time, whereas an average daily dose of 3.06 ± 0.21 mg/kg (plus topical steroids), delivered as intermittent therapy, kept patients in remission for 32% of the time.

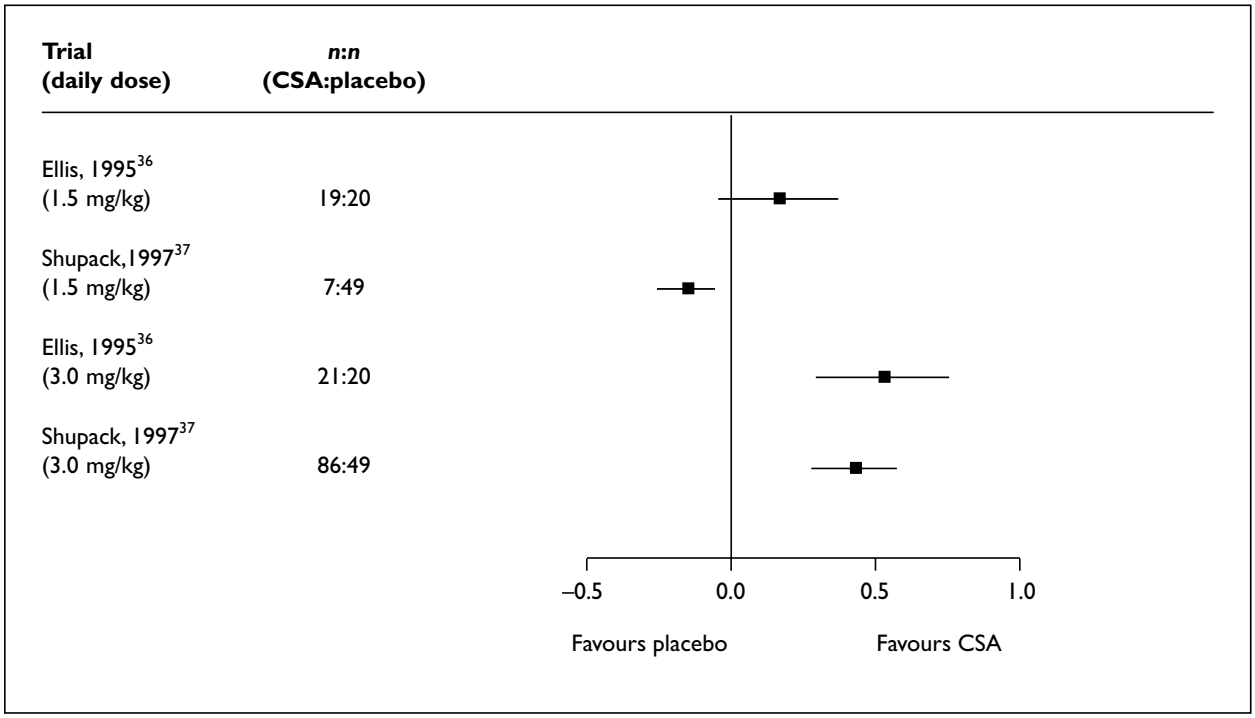

FIGURE 4 *Maintenance treatment with cyclosporin versus placebo: RDs (95% CI)*

Side-effects

Reporting of side-effects was variable. *Tables 11* and *12* summarise the event rates for hypertension and elevated serum creatinine, in studies for which these data were available.

It is well known that cyclosporin is associated with hypertension and renal impairment. The studies included in this review were not primarily designed to address these issues. Long-term observational studies are generally more suitable for estimating the frequency and severity of side-effects.

Discussion

Undoubtedly, the introduction of cyclosporin into the armamentarium available to dermatologists responsible for treating severe psoriasis has been an important advance. This advance was predicated on an understanding of the role that T cells – the target for cyclosporin – play in driving the psoriatic process. Low-dose cyclosporin (2.5–5.0 mg/kg/day) is effective in controlling most cases of severe psoriasis in the short term. Maintenance therapy with low-dose cyclosporin (3.0–3.5 mg/kg/day) is effective in some patients, but there is a move towards the use of low-dose intermittent therapy. This form of therapy involves withdrawing treatment upon clearance and re-instituting treatment upon relapse. It is probable that this approach to treatment may obviate some of the major side-effects associated with long-term continuous therapy, namely hypertension and impairment of renal function. However, a direct comparison of low-dose intermittent therapy versus continuous therapy with cyclosporin for the treatment of severe psoriasis has not been performed. The role of cyclosporin and long-term therapy for severe psoriasis is still unclear, and an RCT comparing this therapy with methotrexate, in particular, has not been performed. We are strongly in favour of such a study.

In clinical practice, cyclosporin is usually used in combination with topical agents such as calcipotriol and topical steroids, and there is some evidence that this approach maximises the efficacy of cyclosporin and keeps the dose required low. RCTs in this review are perforce short-term, and side-effects are not the issue that they would be in long-term studies. Little data are available on the incidence of skin malignancy in patients treated long-term with cyclosporin. This lack of evidence is particularly important, bearing in mind the increased risk of cutaneous squamous cell carcinoma in renal transplant patients receiving this form of immunosuppression.

In summary, cyclosporin is a well-tested treatment for severe psoriasis and in the short term is probably more effective than other forms of systemic therapy.

TABLE 11 *Side-effects of cyclosporin during trials for induction of the remission of psoriasis*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (CSA: comparator)	Number affected of total (proportion)			
					Hypertension (diastolic BP > 90 mmHg)		Elevated creatinine (≥ 130% of baseline)	
					CSA	Comparator	CSA	Comparator
Ellis, 1986[32]	CSA, 14 mg/kg	Placebo	DB, parallel group, 4 weeks	11:10	7 of 11 (0.64)	7 of 10 (0.70)	4 of 11 (0.37)	
Ellis, 1991[17]	CSA, 3.0 mg/kg CSA, 5.0 mg/kg CSA, 7.5 mg/kg	Placebo	DB, parallel group, 8 weeks	25:25 20:25 15:25	See *Notes*		See *Notes*	
Engst, 1989[47]	CSA, 5 mg/kg	Placebo	DB, parallel group, 4 weeks	6:6	2 of 6 (0.33)	1 of 6 (0.17)	0 of 6 (0)	0 of 6 (0)
Guenther, 1991[33]	CSA, 2.5 mg/kg	Placebo	DB, parallel group, 10 weeks	12:11	2 of 12 (0.17)	0 of 11 (0)		
Meffert, 1997[35]	CSA, 1.25 mg/kg CSA, 2.50 mg/kg	Placebo	DB, parallel group, 10 weeks	41:43 44:43	See *Notes*		0 of 41 0 of 44 See *Notes*	0 of 43 See *Notes*
Van Joost, 1988[48]	CSA, 5.5 mg/kg	Placebo	DB, parallel group, 4 weeks	10:10	See *Notes*		See *Notes*	
Finzi, 1993[45]	CSA, 5 mg/kg	Etretinate, 0.75 mg/kg	DB, parallel group, 12 weeks	36:40	7 of 36 (0.19)	1 of 40 (0.025)	6 of 36 (0.17)	2 of 40 (0.05)
Mahrle, 1995[46]	CSA, 2.5 mg/kg	Etretinate, 0.5 mg/kg	SB, parallel group, 10 weeks	140:70	7 of 140 (0.05)			

BP, blood pressure

Trial	Notes
Ellis, 1991[17]	*Changes in BP and creatinine were reported at 8 weeks, but only as the mean percentage change (± SEM) from baseline for the group. Results showed that patients receiving 5.0 or 7.5 mg of CSA had increases in BP statistically different from those of patients in the placebo group. Only patients receiving 7.5 mg of CSA had statistically significant elevations in creatinine. No absolute values were reported*
Meffert, 1997[35]	***Hypertension**: No data for individual patients were reported. The authors stated that, during the DB study period, systolic BP increased by 1.1, 2.4 and 3.7 mmHg in the placebo group and the 1.25- and 2.50-mg/kg/day treatment groups, respectively. Diastolic BP changes were –0.1, 1.8 and 4.4 mmHg, respectively. Overall, five patients developed hypertension (defined as two measurements of diastolic BP > 95 mmHg). Systolic BP values above 160 mmHg occurred in three patients on one occasion only.* ***Creatinine**: There was no dose-dependent overall increase in serum creatinine during the DB study period. In 11 of 133 patients, serum creatinine increased by 30% or more: in four patients, this increase occurred only once; in two patients, it was related to isolated low baseline values; and in the remaining five patients, it was found during the last visit in week 22*
Van Joost, 1988[48]	*Side-effects were reported for the 18 patients who received CSA (i.e. the 10 patients who received it in the DB phase plus eight patients from the placebo group who were given CSA afterwards in the open phase). No comparative data were reported*

continued

TABLE 11 contd *Side-effects of cyclosporin during trials for induction of the remission of psoriasis*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (CSA: comparator)	Number affected of total (proportion)			
					Hypertension (diastolic BP > 90 mmHg)		Elevated creatinine (≥ 130% of baseline)	
					CSA	Comparator	CSA	Comparator
Christophers, 1992[41]	CSA, 1.25 mg/kg CSA, 2.50 mg/kg CSA, 5.00 mg/kg	–	NB, parallel group, 12 weeks	36 121 60	(0.11) (0.21) (0.26)	See *Notes*	(0.01) (0.05) (0.13)	See *Notes*
Laburte, 1994[42]	CSA, 2.5 mg/kg	CSA, 5.0 mg/kg	NB, parallel group, 12 weeks	119:132	See *Notes*		See *Notes*	
Grossman, 1994[34]	CSA, 2 mg/kg, + calcipotriol	CSA, 2 mg/kg, + placebo ointment	DB, parallel group, 6 weeks	35:34	See *Notes*		2 of 35 (0.06)	3 of 34 (0.09)
Elder, 1995[44]	CSA (Neoral), 2.5–5.0 mg/kg	CSA (Sandimmun), 2.5–5.0 mg/kg	DB, crossover (modified), 12 weeks	18:19	See *Notes*		1 of 18	0 of 19
Koo, 1998[43]	CSA (Sandimmun), 2.5 mg/kg	CSA (Neoral), 2.5 mg/kg	DB, parallel group, 12 weeks	152:156	(0.07)	(0.06)	(0.20)	(0.15)

BP, blood pressure

Trial	Notes
Christophers, 1992[41]	*Hypertension and elevated creatinine were reported as the percentage of each group with the side-effect (i.e. no absolute numbers were reported). It was not clear whether intention-to-treat analysis applied*
Laburte, 1994[42]	*It was not possible to identify absolute numbers from the data presented for creatinine. During the course of the study, 55 patients were noted to have hypertension. Two of these patients were already receiving anti-hypertensive medication at the time of entry into the study, 12 patients had elevated BP at the time of the first visit, and hypertension developed in 41 patients during treatment with CSA. Of these 41 patients, 17 were in the group receiving 2.5 mg/kg/day, 20 were receiving 5.0 mg/kg/day, and four were receiving a mean dose of 3.6 mg/kg/day. Twenty-nine patients became hypertensive after the first 3 months of therapy*
Grossman, 1994[34]	*Hypertension was reported in one patient, but no values were given and the group was not identified*
Elder, 1995[44]	*Small but statistically significant elevations of BP were seen with both formulations of CSA. Hypertensive episodes (diastolic BP > 90 mmHg) were not severe, in that most involved BP < 94 mmHg and lasted for < 3 hours*

TABLE 12 *Side-effects of cyclosporin during trials for maintenance of the remission of psoriasis*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (CSA: comparator)	Number affected of total (proportion)			
					Hypertension (diastolic BP > 90 mmHg)		Elevated creatinine (≥ 130% of baseline)	
					CSA	Comparator	CSA	Comparator
Ellis, 1995[36]	CSA, 1.5 mg/kg CSA, 3.0 mg/kg	Placebo	DB, parallel group, 16 weeks	19:20 21:20			0 of 19 (0) 0 of 21 (0)	0 of 20 (0)
Shupack, 1997[37]	CSA, 1.5 mg/kg CSA, 3.0 mg/kg	Placebo	DB, parallel group, 24 weeks	7:49 86:49	(0.09)	(0.09)	17 of 61 (0.28)	6 of 39 (0.15)
Ozawa, 1999[38]	CSA (continuous), 5 mg/kg	CSA (intermittent), 5 mg/kg	NB, parallel group, 36 months minimum	17:20	See *Notes*		See *Notes*	
Ho, 1999[40]	CSA, 2.5–5.0 mg/kg, abruptly discontinued	CSA, 2.5–5.0 mg/kg, dose gradually discontinued	NB, parallel group, 12 months	192:173	45 of 365 (0.12) See *Notes*		See *Notes*	
Zachariae, 1998[39]	CSA (Sandimmun), 3 mg/kg	CSA (Neoral), 3 mg/kg	NB, parallel group, 24 weeks	28:30	4 of 28 (0.14)	6 of 30 (0.20)	5 of 28 (0.18)	6 of 30 (0.20)

Trial	***Notes***
Ozawa, 1999[38]	*Adverse reactions were reported for the whole sample of 94 patients, whereas efficacy data were reported for only the 37 patients who completed at least 36 months of treatment. Increased BP was reported in 21 patients, and increased creatinine in nine patients. The authors reported no differences in the incidence of adverse effects between the two groups*
Ho, 1999[40]	*Adverse reactions were reported for the whole sample. The number and percentage of patients with increased serum creatinine (> 100% of baseline), both on and off treatment, were 6 (1.5%) and 1 (0.3%), respectively. New-onset hypertension occurred in 45 (12%) of patients. One patient experienced severe hypertension, 21 required anti-hypertensive medication, and three discontinued participation in the study because of hypertension*

Chapter 4
Oral retinoids

Summary

In total, 32 RCTs were included in this review of the use of oral retinoids to treat psoriasis: 13 trials concerned the use of etretinate, 11 trials assessed acitretin, and eight trials were comparisons of the two drugs. Of the 32 RCTs, 31 trials concerned the induction of remission, one trial concerned the maintenance of remission, and one trial involved both.

The main outcome was treatment success measured by a specified decrease in PASI or the extent of body surface area involved, or by a global improvement scale. Dichotomous data for effectiveness were analysed using RDs. It was not always possible to pool data because of the marked heterogeneity. Sources of heterogeneity included the initial severity of disease, retinoid dose, success criterion, duration of treatment, the mix of patients included (by psoriasis subtype) and compliance. Some trials also allowed free use of topical steroids, as necessary.

Mucocutaneous side-effects (e.g. cheilitis) are common but usually not dose-limiting. Hyperlipidaemia and hepatitis are recognised side-effects for which patients should be monitored. In women of child-bearing potential, both acitretin and etretinate are probably contraindicated due to the high risk of teratogenicity.

Retinoids appeared to be effective at doses of 75 mg/day or 1 mg/kg/day. Acitretin was as effective as etretinate, with an RD of –0.05 (95% CI, –0.13 to 0.02). Etretinate was less effective than cyclosporin. A retinoid in combination with PUVA was more effective than a retinoid alone, with a pooled RD of 0.12 (95% CI, 0.02 to 0.21). The combination also appeared to require a lower cumulative UVA dose.

Background

The effects of vitamin A and its derivatives (retinoids) on cellular proliferation and differentiation of the skin have long been recognised. Deficiency of vitamin A is associated with hyperkeratosis and squamous metaplasia of mucous membranes, conditions that respond rapidly to administration of the vitamin.[49] Many years ago, dermatologists began to investigate whether supra-physiological doses of vitamin A would benefit patients with hyperkeratinising skin diseases. However, the success rate with vitamin A (retinol) was rather low, and when retinoic acid was used therapeutically, toxic side-effects frequently developed[49] ('hypervitaminosis A syndrome'). This syndrome was characterised by changes in skin and mucous membranes, muscle and joint pains, and headaches. In view of these problems, the search for less toxic vitamin A derivatives began. A number of compounds known as retinoids were developed, and two of these have been subsequently marketed for the treatment of psoriasis. Etretinate was the first to be introduced in the UK and was later replaced by acitretin.

Retinoids, in common with retinoic acid, have numerous effects: troublesome mucocutaneous side-effects, biochemical and metabolic disturbances resulting in raised serum lipids and skeletal hyperostosis, and serious side-effects including hepatotoxicity and teratogenicity. Etretinate is strongly lipophilic and is sequestered in body fat, where it has been detected for as long as 2 years after discontinuation. Typically, it has a half-life of up to 120 days.[50] For these reasons, female patients were advised to continue contraceptive measures for 2 years after discontinuing treatment. Acitretin has a half-life of 50–60 hours and was said to have efficacy similar to that of etretinate.[51] It was initially heralded as the 'safe replacement' for etretinate, but further experience showed that a proportion of the drug could be re-esterified *in vivo*, exposing patients to the risks of etretinate treatment.[52]

Since 1975, a number of reports of the use of retinoid therapy in psoriasis have been published, and recommendations have been made for its use as monotherapy and in combination with various other treatments.

Acitretin is licensed for use in patients with severe, extensive chronic plaque psoriasis that has failed to respond to other treatments. It is also indicated for localised or generalised pustular psoriasis and for erythrodermic psoriasis. At present, the

prescription of acitretin is restricted to hospital dermatology clinics.[53] Etretinate is no longer available in the UK.

Several questions need to be answered to clarify the role of acitretin in the treatment of psoriasis.

1. How effective is acitretin in inducing remission?
2. How effective is acitretin in maintaining remission?
3. What is its role in combination therapy?
4. What are the costs to the patient in terms of adverse effects?
5. How does acitretin compare with other systemic treatments for psoriasis?

Etretinate and acitretin are widely assumed to have actions so similar that acitretin could be freely substituted for etretinate. Different dose regimens and monitoring schemes have been recommended as ways of maximising benefit and minimising harm. In particular, retinoids have been combined with PUVA and occasionally with UVB, in an attempt to minimise the side-effects of both treatments and to improve the therapeutic response. The rate of post-treatment relapse and the existence of a rebound phenomenon are also important practical issues.

Current guidelines for the use of retinoids in psoriasis are not evidence based,[54] and a systematic appraisal of the evidence is required to provide information on which to base future guidelines.

The purpose of this systematic overview is to explore these issues, present the evidence that exists and identify avenues for future research.

Search results

In all, 179 citations were identified for retinoids and psoriasis. Of these, 120 were reports or studies of retinoids, including RCTs, controlled trials (non-randomised), cohort studies, retrospective studies, case reports and small series. Titles and abstracts were reviewed by two people independently (CMC and CEMG) to identify RCTs. Fifty-seven citations appeared to be reports of RCTs; of these citations, 31 concerned the use of etretinate, 24 concerned the use of acitretin, one concerned the use of topical 13-*cis*-retinoic acid, and one concerned the use of tazarotene. All these reports were retrieved and read. Twelve papers were from non-randomised studies, two were subsets of a multicentre study, two contained results that were published in two languages under different lead authors' names, and three contained data that were published more fully elsewhere. In addition, three papers were not from prospective studies (one editorial and two large case series). These 23 reports were excluded from the final list along with the reports of topical treatment with 13-*cis*-retinoic acid or tazarotene (see appendix 2). Therefore, 33 RCTs were available for inclusion in this review.

Characteristics of included studies

These 33 RCTs comprised 31 trials of treatment to induce remission of psoriasis, one trial to maintain remission and one trial that involved both.[45,46,55–85] The characteristics of the trials are summarised in *Tables 13–19*. The trials may be conveniently divided into:

- comparisons of retinoids with placebo (*Table 13*)
- comparisons of acitretin with etretinate (*Table 14*)
- comparisons of retinoid–PUVA combinations versus other treatments (*Table 15*)
- comparisons of retinoid–UVB (broadband or narrowband) combinations versus other treatments (*Table 16*)
- comparisons of retinoid–topical treatment combinations versus other treatments (*Table 17*)
- comparisons of etretinate with cyclosporin (*Table 18*)
- comparison of different dose schedules for acitretin (*Table 19*).

RCTs of retinoids to induce remission of psoriasis

In order to determine whether or not the data from the separate trials could be reasonably pooled statistically, the reports were examined to determine the degree of similarity between them. Thirteen trials concerned the use of etretinate, 11 studies involved acitretin, and a further eight trials were comparisons of the two drugs, either alone or in combination with PUVA (RePUVA). As with the cyclosporin trials, there were considerable variations in the initial severity of the disease, retinoid dose, success criterion and duration of treatment. Other factors that may contribute to the variability of results are the mix of patients (according to disease and gender) and compliance with the dose regimens. Although trials involving patients with chronic plaque psoriasis were selected (and those involving exclusively palmoplantar pustular psoriasis were excluded),

several series contained a small number of patients with palmoplantar pustular psoriasis. One study specifically included patients with guttate psoriasis.[55] The trials included a majority of male patients, although specific exclusions for fertile females were not consistently reported.

Twelve of the 31 trials studying the induction of remission of psoriasis used an objective disease severity criterion for inclusion. Of these 12 trials, 11 used a threshold value for the percentage of body surface area affected (range, 5–20%), and one trial used a threshold PASI value (> 15). The remainder of the studies gave a description, for example, 'severe psoriasis', 'extensive psoriasis' or 'long-standing psoriasis', except for two trials in which there was no explicit criterion.

Sixteen of the studies used an objective (or quasi-objective) criterion for success, such as a 75% decrease in PASI, Psoriasis Severity Index (PSI; a modified PASI) or global score. Four studies did not report a success criterion as such, and the remainder used descriptions such as 'complete remission', 'clear', 'almost clear' or 'markedly improved'.

The daily retinoid dose was described either as a fixed quantity or adjusted to the patient's body weight. Almost all trial protocols allowed some modification of the dose during the trial. Etretinate doses ranged from 30 to 100 mg/day or from 0.5 to 1.0 mg/kg/day. Acitretin doses were 1 mg/kg/day or 10–75 mg/day.

The duration of treatment ranged from 8 to 16 weeks for trials of the induction of remission. One study[56] addressed both the induction and maintenance of remission, reporting results at 2 and 6 months.

RCTs of retinoids to maintain remission

Two trials were concerned with maintenance of the remission of psoriasis. Dubertret and colleagues[57] selected patients with "widespread psoriasis" affecting at least 40% of the body surface area and gave "clearance treatment" that comprised etretinate (1 mg/kg/day) in combination with PUVA, three times per week. If clearance (defined as a 90% reduction in initial clinical score) was achieved within 10 weeks, patients were entered into a randomised comparison of etretinate with placebo over a period of 52 weeks. The etretinate dose used was half the highest dose tolerated during clearance treatment. Both groups received PUVA treatment once a week for the first 2 months of the maintenance treatment phase.

Lassus and colleagues[56] enrolled patients with "long-standing, severe psoriasis" into their study. They compared three different doses of acitretin with placebo both for the induction of remission (8-week phase) and then for maintenance treatment (26-week phase). In addition to the systemic treatment, patients were allowed to use 0.1% difluocortolone valerate ointment.

Results

RCTs comparing retinoids with placebo

Table 20 and *Figure 5* show the success RDs for 11 patient series from six trials for which results were available in a suitable form. The results are statistically heterogeneous. In addition to the factors mentioned above, it should be noted that three of the trial protocols permitted the use of topical steroids.[56–59]

RCTs comparing acitretin with etretinate

Table 21 and *Figure 6* show the success RDs for six patient series from six trials for which results were available in a suitable form. The 95% CI for each of the individual results includes the value of zero, the data are statistically homogeneous, and the pooled value is, as expected, very close to zero. These results show that etretinate and acitretin were equally efficacious in inducing the remission of psoriasis.

RCTs comparing RePUVA with other treatments

Table 22 and *Figure 7* show the success RDs for six patient series from seven trials for which results were available in a suitable form. *Table 23* and *Figure 8* show the corresponding mean differences in the number of PUVA treatments (insufficient data were available to compare mean differences in the 'time to clearance' or the total PUVA doses). Only one trial demonstrated a difference in success rates for RePUVA versus PUVA. The data were statistically homogeneous, and the pooled value shows a small increase in the success rate for RePUVA treatment. The corresponding data for PUVA exposure were reported differently in the different studies, therefore it was not possible to demonstrate a consistent reduction in PUVA exposure (e.g. reduction in total PUVA dose or reduction in the time to clearance). *Figure 8* shows that, in five trials for which results were available, there was a clear trend towards a reduction in the UVA dose required. Differences in the way in which the data were collected may account for the observed heterogeneity.

RCTs comparing etretinate with cyclosporin

Table 24 and *Figure 9* show the success RDs for two patient series from two RCTs. These were both large studies, and the results clearly show that etretinate was less efficacious in inducing remission of psoriasis than was cyclosporin. Nevertheless, it should be noted that the response rate to etretinate in the study by Finzi and colleagues[45] was 0.73 (73%). This study used a daily etretinate dose of 0.75 mg/kg, whereas a dose of 0.5 mg/kg was used in the study by Mahrle and colleagues.[46]

RCTs comparing retinoid–UVB (broadband or narrowband) combinations versus other treatments

Table 25 and *Figure 10* shows the success rates in five patient series from four trials for which results were available in a suitable form. Two series compared a retinoid and UVB combination with UVB alone.[55,60] On each occasion, the combination appeared to be superior to phototherapy alone. Iest and Boer[61] compared the combination of acitretin and UVB with acitretin alone and with UVB alone. In each case, the combination was superior to the single treatment. Green and colleagues[55] also compared a retinoid and UVB combination with a retinoid and PUVA combination, and they reported no difference in success rates.

RCTs comparing retinoid–topical treatment combinations versus other treatments

Table 26 and *Figure 11* show the success RDs for six patient series from four trials. Three series compared a combination of retinoid and topical steroid with a topical steroid (and placebo), and two series compared the combination with systemic retinoid and placebo cream or ointment. In four of the series, the combination was superior to the single treatment.

One series compared the combination of acitretin and calcipotriol with acitretin and placebo ointment.[62] Once again, the combination was superior to the single treatment.

RCTs of retinoids to maintain remission of psoriasis

Dubertret and colleagues[57] showed that relapses occurred more frequently in the placebo-treated group than in the etretinate-treated group (see *Table 22*). Lassus and colleagues[56] treated four groups of patients with acitretin (10, 25 or 50 mg/day) or placebo for a period of 6 months and recorded the PASI each month (*Table 13*). After 6 months, there were no differences between the four groups. The authors point out that the final evaluation was carried out in the summer when many patients experience "at least partial spontaneous remission"; however, patients were also allowed to use steroid ointment as required.

Side-effects

Side-effects were reported in a number if different ways, making it difficult to make direct comparisons between trials. Most authors commented that skin and mucous membrane effects were common among patients receiving retinoids.

Discussion

This review confirmed that acitretin was as effective as etretinate in the treatment of chronic plaque psoriasis, and therefore it seemed justified to combine the results.

Comparisons of retinoids with placebo produced very variable results that can be explained, in part, by the small numbers in the study by Goldfarb and co-workers.[65] A suggestion of a dose–response relationship is discernible, with doses below 75 mg/day or 1 mg/kg/day generally performing no better than placebo. However, the results will also have been influenced by the effects of concurrent topical steroid treatment (in studies reported by Lassus in 1980,[58] Melis in 1984,[59] and Lassus and co-workers in 1987[56]) and the mix of patients (by psoriasis type).

The combination of retinoid and PUVA (rePUVA) has been recommended by leading dermatologists for some time, and this review confirms that the combination is not only superior to PUVA alone but also appears to permit a reduction in the cumulative UVA dose required. The combination of retinoid with UVB or, more recently, narrowband UVB (NBUVB) is less well known, but it may offer a safer alternative to rePUVA. This review showed that the combinations of retinoid plus UVB or retinoid plus NBUVB were both more effective than the retinoid alone. Two of the three relevant studies[60,61,81] (Iest and Boer,[61] and Ruzicka and co-workers[60]) achieved positive results using low doses of retinoid (30 or 35 mg/day of acitretin). Only one study[55] compared the retinoid plus NBUVB combination with rePUVA, and no differences in efficacy were reported. This combination may be an important avenue for future research, given the perceived advantages of

NBUVB and the possibility that lower systemic retinoid doses may be required (see chapter 6). When compared with cyclosporin, etretinate appeared to be relatively ineffective, but the individual response rates tell a different story. In one study,[45] etretinate was given at a dose of 0.75 mg/kg/day, resulting in a success rate of 0.73. When a dose of 0.5 mg/kg/day was used, the success rate was only 0.16.

Combinations of systemic retinoids with topical treatments involved either steroids[82–84] or calcipotriol.[62] These studies generally had larger numbers of participants than the other studies in this review, and the results suggested a clear trend in favour of the combinations. However, it should be noted that the end-points of these trials were subjective for the most part.

Subjective mucocutaneous side-effects are limiting, as are concerns over hyperlipidaemia and teratogenicity. Overall, systemic retinoids (i.e. acitretin and etretinate) are only modestly effective as a monotherapy for severe psoriasis, but this efficacy is enhanced by higher, albeit often intolerable doses.

TABLE 13 *Design of trials of acitretin or etretinate versus placebo*

Trial	Intervention (daily dose)	Comparator	Design and duration	*n*:*n* (retinoid:placebo)	Inclusion criterion (disease severity)	Success criterion
Induction of remission of psoriasis						
Jakubowicz, 1986[63]	Etretinate, 1 mg/kg	Placebo	DB, parallel group, 16 weeks	15:15	Not reported	Almost or complete remission
Lassus, 1980[58]	Etretinate, 50 mg See *Notes*	Placebo	DB, crossover, 52 weeks See *Notes*	48:49	"Psoriasis of long duration"	Complete remission
Melis, 1984[59]	Etretinate, 1 mg/kg	Placebo	DB, parallel group, 10 weeks	15:15	> 5% BSA affected	Marked improvement or complete remission
Wolska, 1983[64]	Etretinate, 1 mg/kg	Placebo	DB, parallel group, 16 weeks	20:20	"Severe psoriasis"	Almost or complete clearing
Goldfarb, 1988[65]	Acitretin, 10 mg Acitretin, 25 mg Acitretin, 50 mg Acitretin, 75 mg	Placebo	DB, parallel group, 8 weeks	5:12 5:12 11:12 5:12	> 10% BSA affected	≥ 75% improvement in global score
Kingston, 1987[66]	Acitretin, 10 mg Acitretin, 50 mg Acitretin, 75 mg	Placebo	DB, parallel group, 8 weeks	5:6 5:6 5:6	> 20% BSA affected	≥ 75% clearing of psoriatic plaques
Lassus, 1987[56]	Acitretin, 10 mg Acitretin, 25 mg Acitretin, 50 mg	Placebo	DB, parallel group, 8 weeks See *Notes*	20:20 20:20 20:20	"Long-standing severe psoriasis"	≥ 75% decrease in PASI, or PASI < 8
Madhok, 1987[67]	Acitretin, 25 mg Acitretin, 50 mg	Placebo	DB, parallel group, 8 weeks	2:3 3:3	> 15% BSA affected	Not reported for DB phase of study
Olsen, 1989[68]	Acitretin, 25 mg Acitretin, 50 mg	Placebo	DB, parallel group, 8 weeks	4:5 6:5	> 10% BSA affected	Not reported
Maintenance of remission of psoriasis						
Dubertret, 1985[57]	Etretinate, 1 mg/kg	Placebo	DB, parallel group, 52 weeks	16:20	Psoriasis cleared (< 10% of initial global clinical score) by etretinate (1mg/kg/day) + PUVA, three times per week	Absence of relapse (clinical score > 50% of initial score)
Lassus, 1987[56]	Acitretin, 10 mg Acitretin, 25 mg Acitretin, 50 mg	Placebo	DB, parallel group, 26 weeks See *Notes*	20:20 20:20 20:20	"Long-standing severe psoriasis"	Not reported

Trial	***Notes***
Lassus, 1980[58]	*Patients received 100 mg/day for the first 2 weeks and then a maintenance dose of 50 mg/day. The DB, pre-crossover, 13-week phase was used for analysis*
Lassus, 1987[56]	*The study covered both the induction and maintenance of remission. The initial 8-week phase produced results for assessing the induction of remission. Maintenance treatment was assessed at 26 weeks. The authors commented that "after 6 months the difference in efficacy between placebo and the different doses of etretin (acitretin) was no longer significant"*

TABLE 14 *Design of trials comparing acitretin with etretinate*

Trial	Intervention (daily dose)	Comparator (daily dose)	Design and duration	*n*:*n* (acitretin:etretinate)	Inclusion criterion (disease severity)	Success criterion
Gollnick, 1988[69]	Acitretin, 10 mg Acitretin, 25 mg Acitretin, 50 mg	Etretinate, 50 mg	DB, parallel group, 8 weeks	46:43 43:43 43:43	> 20% BSA affected	≥ 75% decrease in PASI (or PSI[†])
Bauer, 1993[70]	Acitretin, 50 mg	Etretinate, 50 mg	DB, parallel group, 12 weeks	71:74	"Severe psoriasis"	≥ 75% decrease in PSI[‡]
Gollnick, 1993[71 *]	Acitretin, 50 mg	Etretinate, 50 mg	DB, parallel group, 24 weeks	71:74		
Kragballe, 1989[72]	Acitretin, 40 mg	Etretinate, 40 mg	DB, parallel group, 12 weeks	127:41	"Long-standing severe psoriasis"	Marked or total clearance
Ledo, 1988[73]	Acitretin, 30 mg	Etretinate, 30 mg	DB, parallel group, 12 weeks	10:10	"Severe psoriasis"	Not reported
Meffert, 1989[74]	Acitretin, 30 mg	Etretinate, 30 mg	DB, parallel group, 12 weeks	10:10	"Severe psoriasis"	Marked improvement or remission

PSI, Psoriasis Severity Index

[*] *A follow-up study of the patients in Bauer, 1993*[70]

[†] *"Corrected PASI"; range, 0–36*

[‡] *Sum of the intensity of erythema, infiltration and scaling on the head, trunk, arms and legs, with a range of 0–4 for each; total range, 0–48*

TABLE 15 *Design of trials of retinoids (acitretin or etretinate) combined with PUVA (RePUVA)*

Trial	Intervention	Comparator	Design and duration	*n:n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Parker, 1984[75]	Etretinate, 0.75 mg/kg, + PUVA	PUVA + placebo	NB, parallel group, 10 weeks	15:15	> 20% BSA affected	Clearance (< 2% BSA affected)
Lauharanta, 1981[76]	Etretinate, 60 mg/day for 4 weeks Then etretinate + PUVA for 6 weeks	PUVA	NB, parallel group, 10 weeks	20:20	"Severe psoriasis"	≥ 75% decrease in PASI
		Etretinate, 60 mg/day		20:20		
		Etretinate, 60 mg/day, for 4 weeks Then PUVA for 6 weeks		20:20		
Green, 1992[55]	Etretinate, 1 mg/kg, + PUVA	Etretinate + NBUVB	NB, parallel group, variable duration	15:15	"Extensive chronic plaque or guttate psoriasis"	"Satisfactory response"
		NBUVB		15:15		
Lauharanta, 1989[77]	Acitretin, 40 mg/day, + bath PUVA	Etretinate, 40 mg/day, + bath PUVA	DB, parallel group, 10 weeks	17:17	"Widespread plaque-type psoriasis"	≥ 90% decrease in PASI
Saurat, 1988[78]	Etretinate, 50 mg/day, + PUVA	PUVA + placebo	DB, parallel group, 12 weeks	23:22	Severe psoriasis with > 20% BSA affected, or erythrodermic psoriasis	≥ 75% decrease in PASI
	Acitretin, 50 mg/day, + PUVA			20:22		
Sommerburg, 1993[79]	Acitretin, 50 mg/day, + PUVA	PUVA + placebo	DB, parallel group, 8 weeks	44:44	"Generalized chronic plaque psoriasis severe enough to require PUVA"	≥ 75% decrease in PSI*
Tanew, 1991[80]	Acitretin, 1 mg/kg, + PUVA	PUVA + placebo	DB, parallel group, 11 weeks	30:30	"Severe and extensive psoriasis – > 20% BSA"	≥ 90% clearance of psoriasis
Maintenance of remission of psoriasis						
Dubertret, 1985[57]	Etretinate, 0.5 mg, + PUVA once weekly for 2 months	Placebo + PUVA once weekly for 2 months	DB, parallel group, 52 weeks	16:20	Psoriasis cleared (< 10% of initial global clinical score) by etretinate, 1 mg/kg/day, + PUVA three times per week	Absence of relapse (clinical score > 50% of initial score)

* *PSI scale, 0–36*

TABLE 16 *Design of trials of retinoids (acitretin or etretinate) combined with broadband or narrowband UVB*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Green, 1992[55]	Etretinate, 1 mg/kg, + NBUVB	NBUVB	NB, parallel group, variable duration	15:15	"Extensive chronic plaque or guttate psoriasis"	"Satisfactory response"
		Etretinate, 1 mg/kg, + PUVA		15:15		
Iest, 1989[61]	Acitretin + UVB	Acitretin	NB, parallel group, left/right, 30 exposures	9:9	Chronic plaque psoriasis with ≥ 10% BSA affected	≥ 80% clearance
		UVB		9:32		
Lowe, 1991[81]	Acitretin, 50 mg/day, + UVB	UVB + placebo	NB, parallel group, 12 weeks	16:18	Moderate–severe psoriasis with > 20% BSA affected	Not reported
Ruzicka, 1990[60]	Acitretin, 35 mg/day, + UVB	UVB + placebo	DB, parallel group, 8 weeks	40:38	Generalised chronic plaque or "exanthematous"-type psoriasis severe enough to require combination treatment	≥ 75% decrease in PASI

TABLE 17 *Design of trials of retinoids (acitretin or etretinate) combined with topical treatment*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Retinoid combined with steroids						
Binazzi, 1981[82]	Etretinate + difluocortolone valerate 0.1% ointment	Difluocortolone valerate 0.1% ointment + placebo	DB, parallel group, variable duration	30:30	Not reported ("patients with psoriasis")	≥ 75% decrease in total score (scale, 0–16)
Christiansen, 1982[83]	Etretinate, 1 mg/kg, + betamethasone valerate 0.1% cream	Etretinate + placebo cream	DB, parallel group, 8 weeks	50:50	"Patients with psoriasis vulgaris"	Complete or satisfactory remission
		Betamethasone valerate 0.1% cream + placebo		50:46		
van der Rhee, 1980[84]	Etretinate, 0.66 mg/kg, + triamcinolone acetonide 0.1% and salicylic acid cream	Etretinate + placebo cream	DB, parallel group, 6 weeks	30:30	> 15% BSA affected	Overall improvement
		Triamcinolone acetonide 0.1% and salicylic acid cream + placebo		30:30		
Retinoid combined with calcipotriol						
van de Kerkhof, 1998[62]	Acitretin, 20 mg/day, + calcipotriol	Acitretin, 20 mg/day, + placebo cream	DB, parallel group, 12 weeks	76:59	"Severe or extensive psoriasis vulgaris...not responsive to topical treatment alone"	Clearance or marked improvement

TABLE 18 *Design of trials of etretinate versus cyclosporin*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (etretinate:CSA)	Inclusion criterion (disease severity)	Success criterion
Finzi, 1993[45]	Etretinate, 0.75 mg/kg	CSA, 5.0 mg/kg	DB, parallel group, 12 weeks	40:36	PASI > 15	≥ 75% decrease in PASI, or PASI < 8
Mahrle, 1995[46]	Etretinate, 0.5 mg/kg	CSA, 2.5 mg/kg	SB, parallel group, 10 weeks	70:140	"Moderate–severe"	≥ 70% decrease in PASI

TABLE 19 *Trial of different dosage schedules for acitretin*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion	Response rate
Berbis, 1989[85]	Acitretin, increasing dose	Acitretin, constant dose	DB, parallel group, 6 weeks	22:27	Not reported ("patients with psoriasis")	Not reported	Not extractable
		Acitretin, decreasing dose	DB, parallel group, 6 weeks	22:25			

TABLE 20 *Treatment success RDs: retinoids compared with placebo*

Trial	Intervention (daily dose)	Comparator	*n:n* (retinoid:placebo)	Success criterion	Response rate (retinoid:placebo)	RD (95% CI)
Induction of remission of psoriasis						
Jakubowicz, 1986[63]	Etretinate, 1 mg/kg	Placebo	15:15	Almost or complete remission	7/15:0/15	0.47 (0.00 to 0.72)
Lassus, 1980[58]	Etretinate, 50 mg	Placebo	48:49	Complete remission	8/48:3/49	0.11 (–0.02 to 0.24)
Melis, 1984[59]	Etretinate, 1 mg/kg	Placebo	15:15	Marked improvement or complete remission	13/15:0/15	0.87 (0.07 to 1.04)
Wolska, 1983[64]	Etretinate, 1 mg/kg	Placebo	20:20	Almost or complete clearing	7/20:1/20	0.30 (0.07 to 0.53)
Goldfarb, 1988[65]	Acitretin, 10 mg	Placebo	5:12	≥ 75% improvement in global score	0/5:1/12	–0.08 (–0.23 to 0.07)
	Acitretin, 25 mg		5:12		0/5:1/12	–0.08 (–0.23 to 0.07)
	Acitretin, 50 mg		11:12		2/11:1/12	0.10 (–0.17 to 0.37)
	Acitretin, 75 mg		5:12		2/5:1/12	0.32 (–0.14 to 0.78)
Kingston, 1987[66]	Acitretin, 10 mg	Placebo	5:6	≥ 75% clearing of psoriatic plaques	Not extractable	*
	Acitretin, 50 mg		5:6		Not extractable	*
	Acitretin, 75 mg	Placebo	5:6		Not extractable	*
Lassus, 1987[56]	Acitretin, 10 mg,	Placebo	20:20	≥ 75% decrease in PASI, or PASI < 8	8/20:5/20	0.15 (–0.14 to 0.44)
	Acitretin, 25 mg		20:20		12/20:5/20	0.35 (0.06 to 0.64)
	Acitretin, 50 mg		20:20		14/20:5/20	0.45 (0.17 to 0.73)
Madhok, 1987[67]	Acitretin, 25 mg	Placebo	2:3	Not reported for DB phase of study	Not extractable	*
	Acitretin, 50 mg		3:3			
Olsen, 1989[68]	Acitretin, 25 mg	Placebo	4:5	Not reported	Not extractable	*
	Acitretin, 50 mg		6:5			

* *As data were not extractable, it was not possible to calculate RDs for these studies*

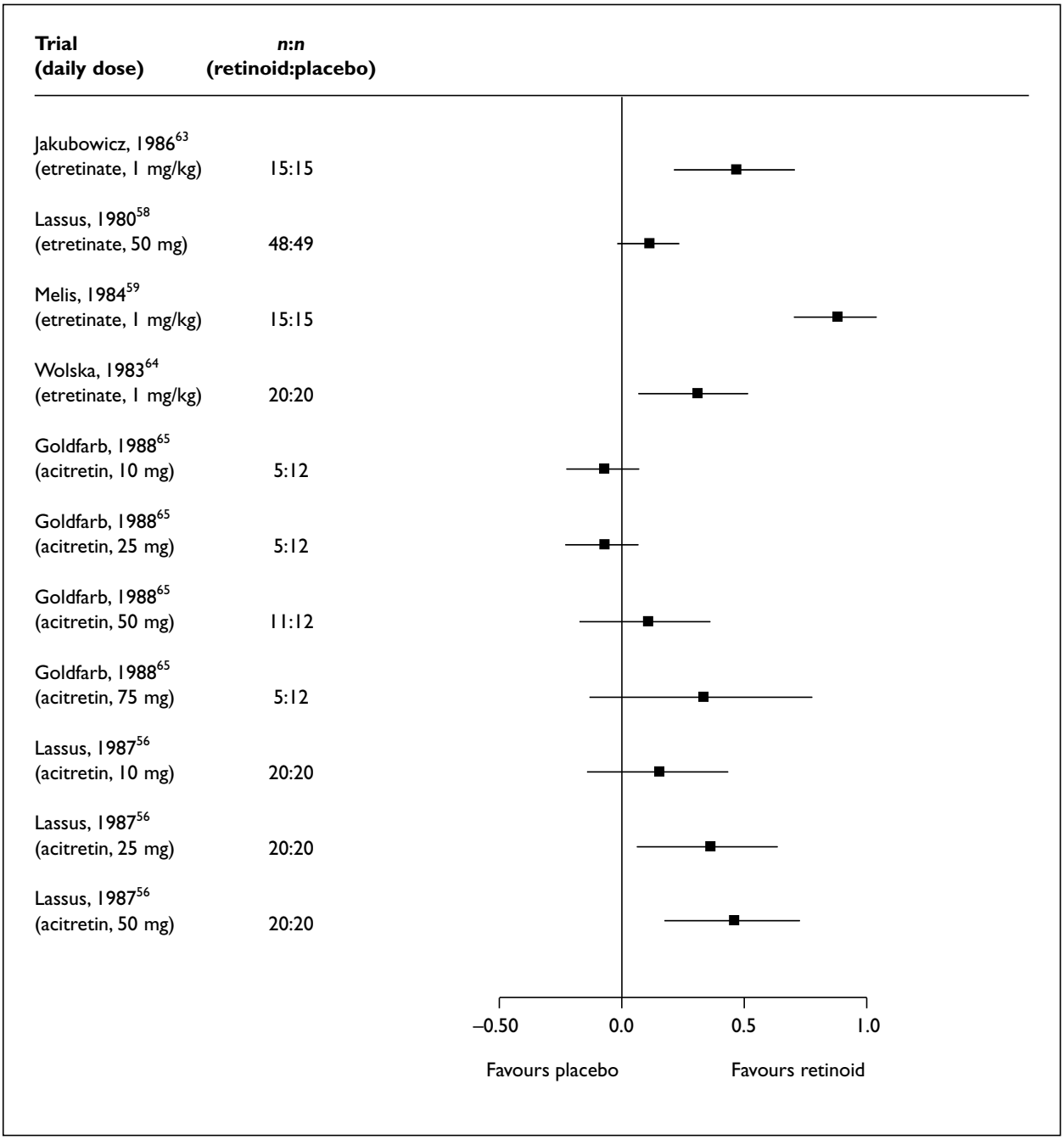

FIGURE 5 *Retinoids versus placebo: RDs (95% CI)*

TABLE 21 *Treatment success RDs: acitretin compared with etretinate*

Trial	Intervention (daily dose)	Comparator (daily dose)	*n:n* (acitretin:etretinate)	Success criterion	Response rate (acitretin:etretinate)	RD (95% CI)
Gollnick, 1988[69]	Acitretin, 10 mg	Etretinate, 50 mg	46:43	≥ 75% decrease in PASI (or PSI[†])	0.250:0.361	–0.11 (–0.30 to 0.08)
	Acitretin, 25 mg		43:43		0.216:0.361	–0.14 (–0.33 to 0.05)
	Acitretin, 50 mg		43:43		0.231:0.361	–0.13 (–0.32 to 0.06)
Bauer, 1993[70]	Acitretin, 50 mg	Etretinate, 50 mg	71:74	≥ 75% decrease in PSI[‡]	29/71:23/74	0.10 (–0.06 to 0.26)
Gollnick, 1993[71] *	Acitretin, 50 mg	Etretinate, 50 mg	71:74		Not extractable	
Kragballe, 1989[72]	Acitretin, 40 mg	Etretinate, 40 mg	127:41	Marked or total clearance	94/127:31/41	–0.02 (–0.17 to 0.13)
Ledo, 1988[73]	Acitretin, 30 mg	Etretinate, 30 mg	10:10	Not reported	Not extractable	
Meffert, 1989[74]	Acitretin, 30 mg	Etretinate, 30 mg	10:10	Marked improvement or remission	1/10:3/10	–0.20 (–0.54 to 0.14)

[*] *A follow-up study of the patients in Bauer, 1993*[70]
[†] *"Corrected PASI"; range, 0–36*
[‡] *Sum of the intensity of erythema, infiltration and scaling on the head, trunk, arms and legs, with a range of 0–4 for each; total range, 0–48*

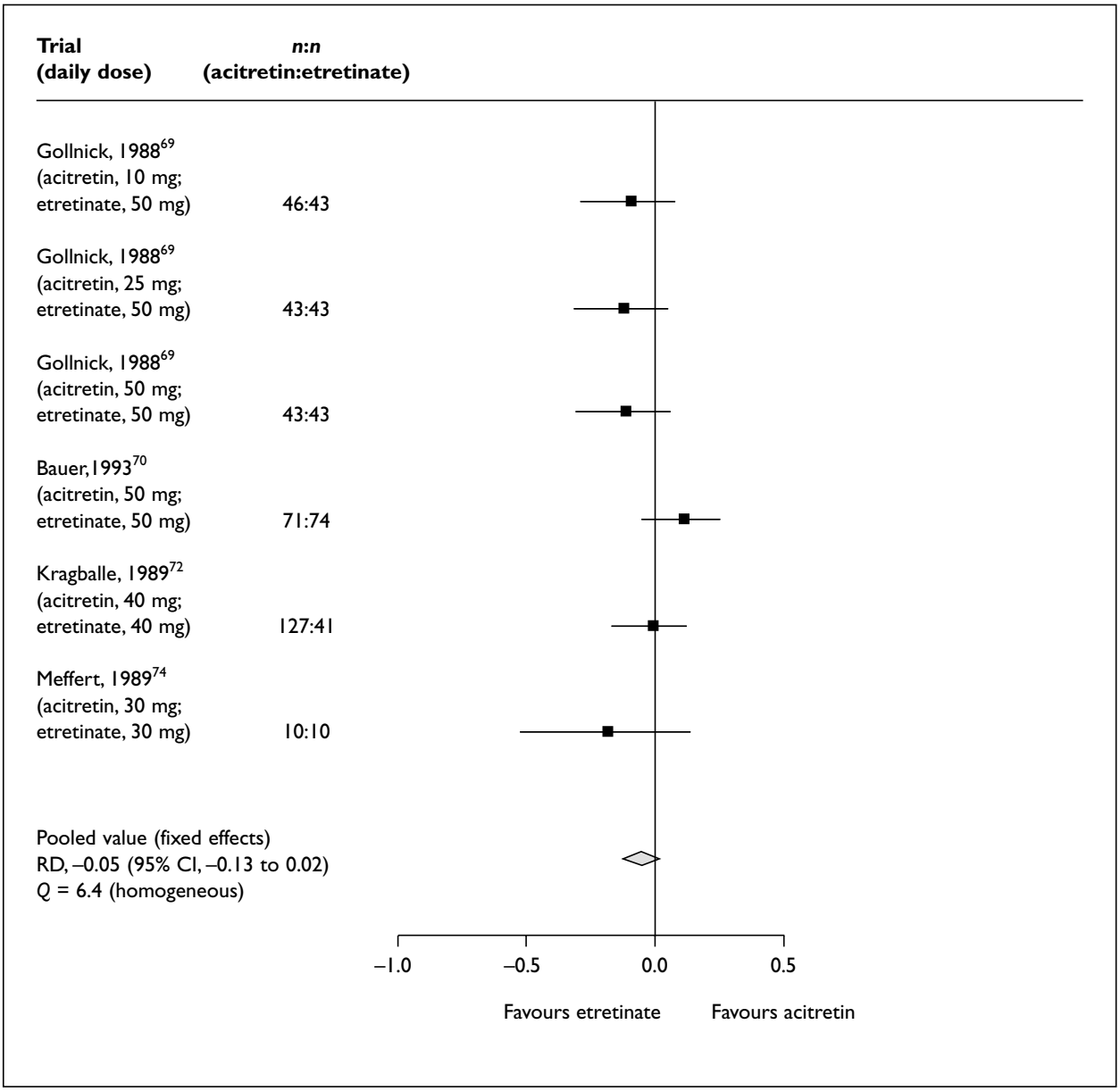

FIGURE 6 *Acitretin versus etretinate: RDs (95% CI)*

TABLE 22 *Treatment success RDs: trials of retinoids (acitretin or etretinate) combined with PUVA (RePUVA)*

Trial	Intervention	Comparator	*n:n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Parker, 1984[75]	Etretinate, 0.75 mg/kg, + PUVA	PUVA + placebo	15:15	Clearance (< 2% BSA affected)	14/15:9/15	0.33 (0.05 to 0.61)
Lauharanta, 1981[76]	Etretinate, 60 mg/day, for 4 weeks Then etretinate + PUVA for 6 weeks	PUVA	20:20	≥ 75% decrease in PASI	16/20:16/20	0.00 (–0.25 to 0.25)
		Etretinate, 60 mg/day	20:20			
		Etretinate, 60 mg/day, for 4 weeks Then PUVA for 6 weeks	20:20			
Green, 1992[55]	Etretinate, 1 mg/kg, + PUVA	Etretinate + NBUVB	15:15	"Satisfactory response"	15/15:14/15	
		NBUVB	15:15		15/15:12/15	
Lauharanta, 1989[77]	Acitretin, 40 mg/day, + bath PUVA	Etretinate, 40 mg/day, + bath PUVA	17:17	≥ 90% decrease in PASI	17/17:17/17	
Saurat, 1988[78]	Etretinate, 50 mg/day, + PUVA	PUVA + placebo	23:22	≥ 75% decrease in PASI	16/23:16/22	0.12 (–0.12 to 0.36)
	Acitretin, 50 mg/day, + PUVA		20:22		17/20:16/22	0.15 (–0.10 to 0.40)
Sommerburg, 1993[79]	Acitretin, 50 mg/day, + PUVA	PUVA + placebo	44:44	≥ 75% decrease in PSI	28/44:19/44	0.20 (–0.01 to 0.41)
Tanew, 1991[80]	Acitretin, 1 mg/kg, + PUVA	PUVA + placebo	30:30	≥ 90% clearance of psoriasis	22/30:20/30	0.06 (–0.17 to 0.29)
Maintenance of remission of psoriasis						
Dubertret, 1985[57]	Etretinate, 0.5 mg, + PUVA once weekly for 2 months	Placebo + PUVA once weekly for 2 months	16:20	Absence of relapse (clinical score > 50% of initial score)	9/16:3/20	0.41 (0.12 to 0.70)

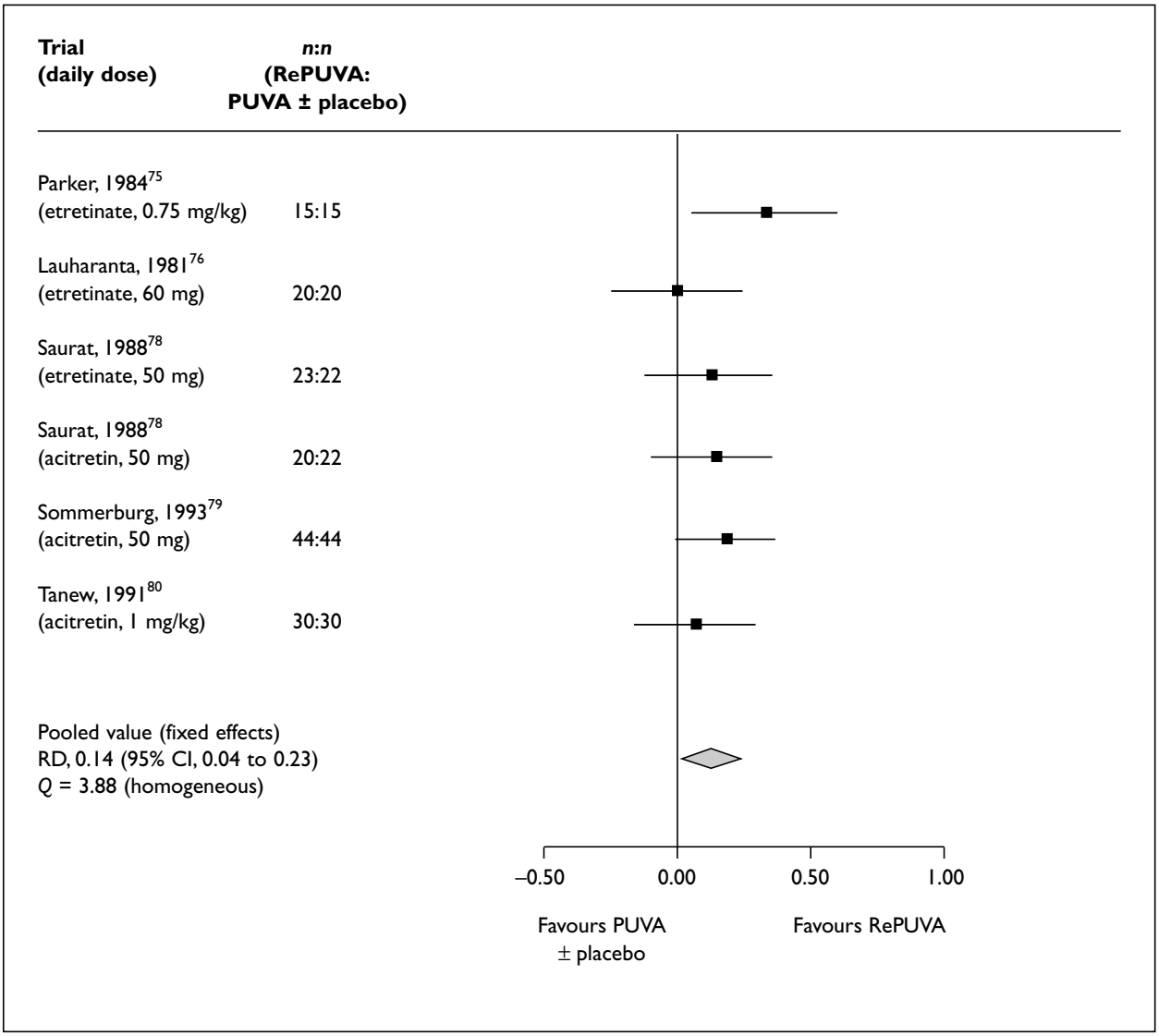

FIGURE 7 *RePUVA versus PUVA ± placebo: RDs (95% CI)*

TABLE 23 *Comparison of RePUVA combination with PUVA ± placebo: dose of UVA*

Trial	*n*:*n* (RePUVA:PUVA)	Retinoid	Response rate (RePUVA:PUVA)	Mean UVA dose (J/cm^2) (RePUVA:PUVA)	Difference in mean UVA doses (J/cm^2) (95% CI)
Parker, 1984[75]	15:15	Etretinate	0.93:0.60	62.1 ± 9.0:77.3 ± 14.8 (± SEM)	15.2 (–18.8 to 49.2)
Lauharanta, 1981[76]	20:20	Etretinate	0.80:0.80	66.9 ± 18.7:199.5 ± 46.8 (± SD)	132.6 (110.5 to 154.7)
Saurat, 1988[78]	23:22 20:22	Etretinate Acitretin	0.85:0.73 0.70:0.73	57.8 ± 5.4:97.2 ± 12.2 (± SEM) 73.7 ± 10.5:97.2 ± 12.2 (± SEM)	39.4 (13.3 to 65.5) 23.5 (–8.0 to 55.0)
Tanew, 1991[80]	30:30	Acitretin	0.73:0.67	58.7 ± 17.9:101.5 ± 15.8 (± SEM)	42.8 (–4.0 to 89.6)

SD, standard deviation

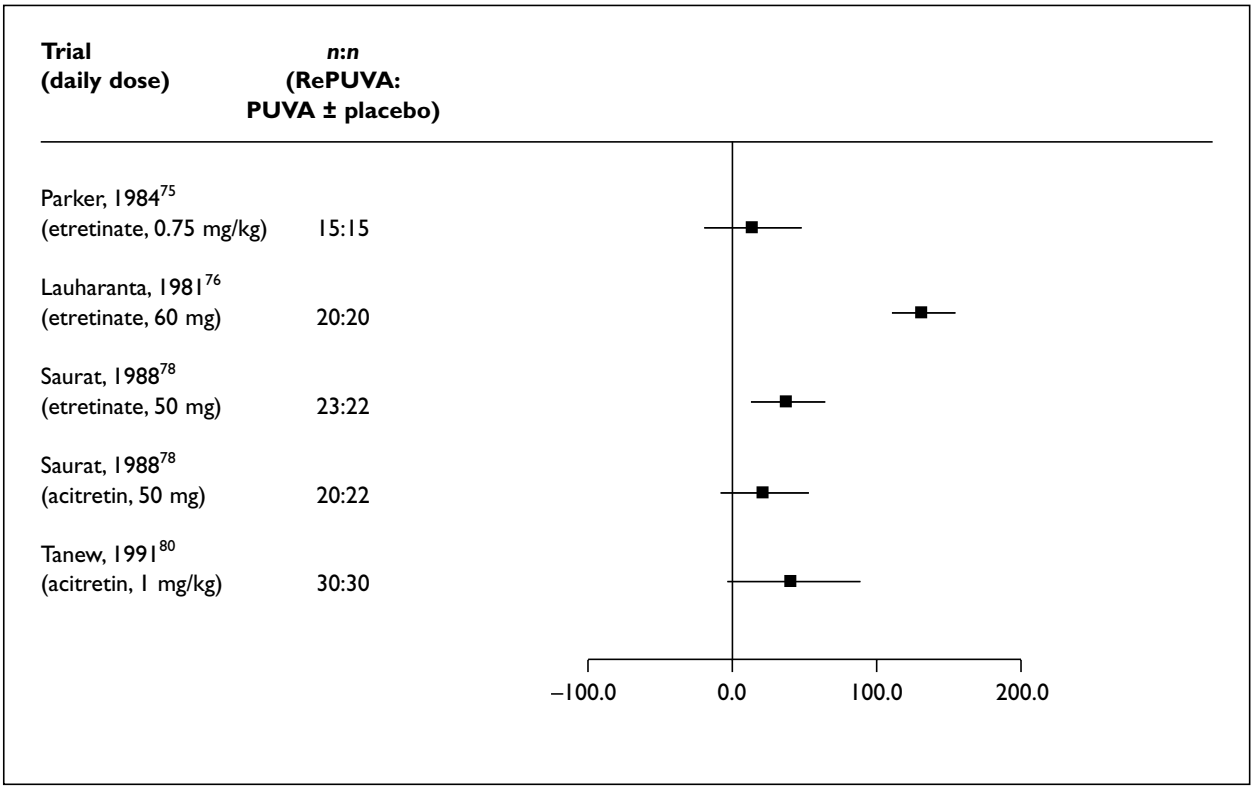

FIGURE 8 *RePUVA versus PUVA ± placebo: mean decrease in UVA dose (in J/cm^2)*

TABLE 24 *Treatment success RDs: trials of etretinate versus cyclosporin*

Trial	Intervention (daily dose)	Comparator (daily dose)	*n:n* (etretinate:CSA)	Success criterion	Response rate (etretinate:CSA)	RD (95% CI)
Finzi, 1993[45]	Etretinate, 0.75 mg/kg	CSA, 5.0 mg/kg	40:36	≥ 75% decrease in PASI, or PASI < 8	0.73:0.97	–0.24 (–0.39 to –0.09)
Mahrle, 1995[46]	Etretinate, 0.5 mg/kg	CSA, 2.5 mg/kg	70:140	≥ 70% decrease in PASI	0.16:0.62	–0.46 (–0.58 to –0.34)

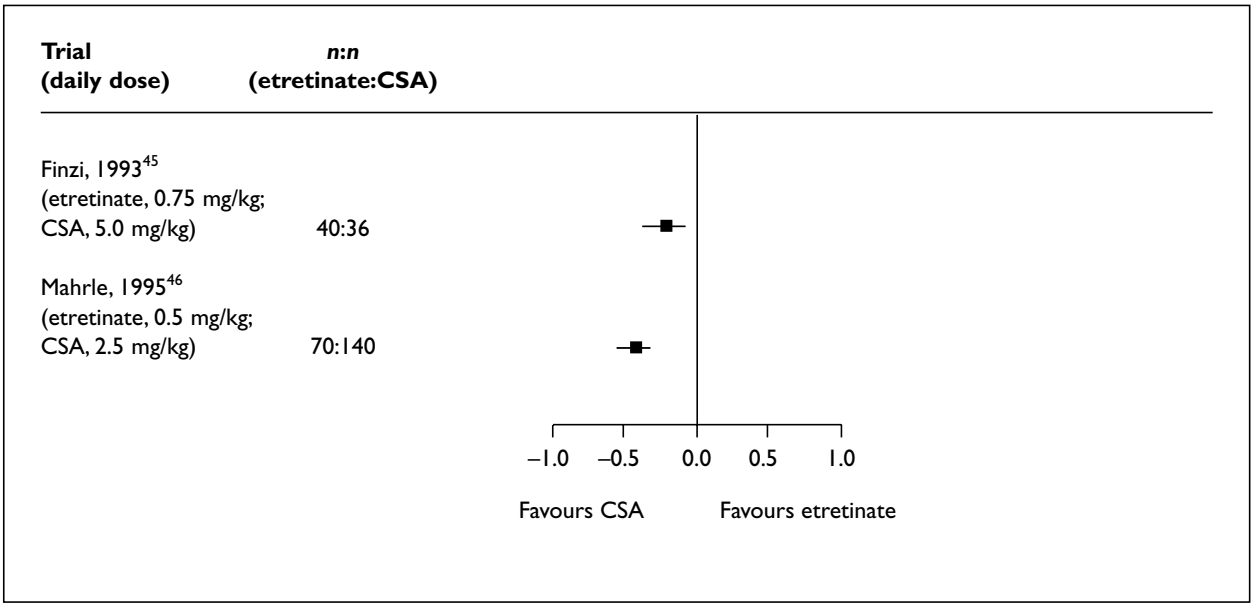

FIGURE 9 *Etretinate versus cyclosporin: RDs (95% CI)*

TABLE 25 *Treatment success RDs: trials of retinoids (acitretin or etretinate) combined with BBUVB or NBUVB*

Trial	Intervention	Comparator	*n:n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Green, 1992[55]	Etretinate, 1 mg/kg, + NBUVB	NBUVB + placebo	15:15	"Satisfactory response"	14/15:12/15	0.33 (0.05 to 0.61)
		Etretinate, 1 mg/kg, + PUVA	15:15		14/15:15/15	–0.07 (–0.20 to 0.06)
Iest, 1989[61]	Acitretin + UVB	Acitretin	9:9	≥ 80% clearance	8/9:2/9	0.67 (0.33 to 1.01)
		UVB	9:32		8/9:20/32	0.26 (0.00 to 0.52)
Lowe, 1991[81]	Acitretin, 50 mg/day, + UVB	UVB + placebo	16:18	Not reported	Not extractable	
Ruzicka, 1990[60]	Acitretin, 35 mg/day, + UVB	UVB + placebo	42:40	≥ 75% decrease in PASI	24/42:9/40	0.34 (0.14 to 0.54)

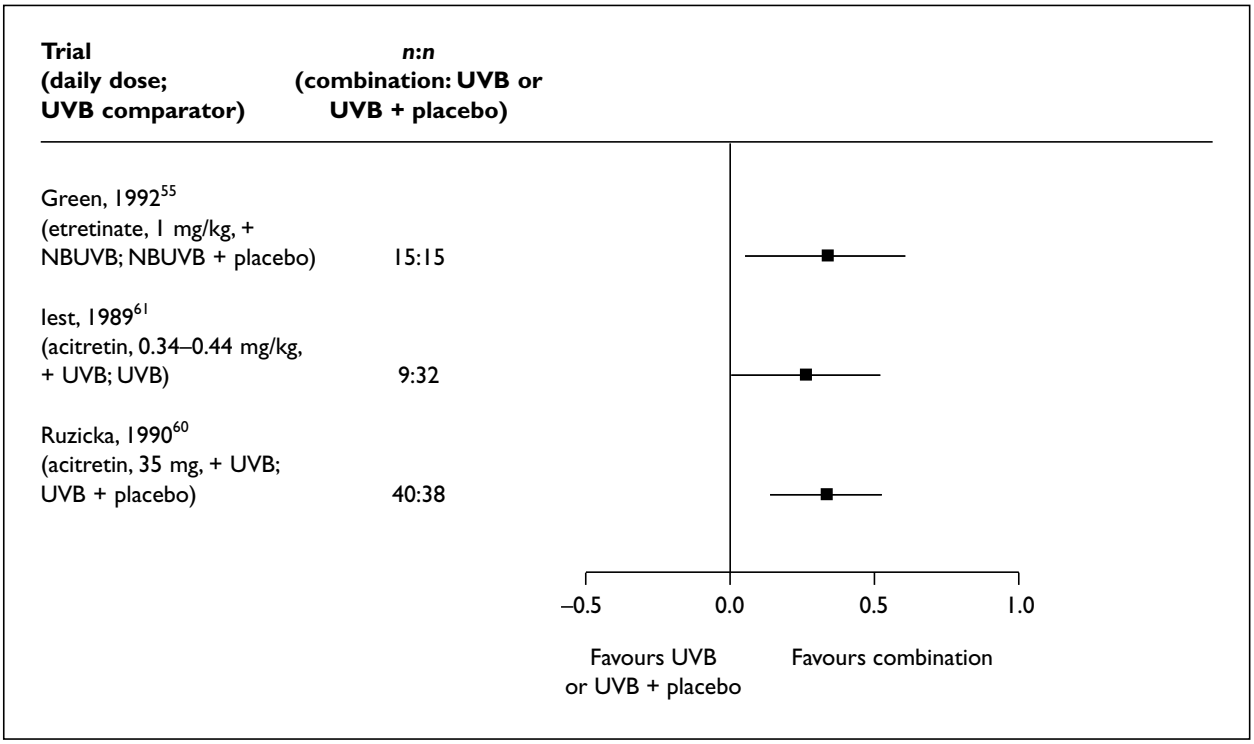

FIGURE 10 *Retinoid and UVB combinations versus UVB: RDs (95% CI)*

TABLE 26 *Treatment success RDs: trials of retinoids (acitretin or etretinate) combined with topical treatment*

Trial	Intervention	Comparator	*n:n* (intervention: comparator)	Success criterion	Response rate	RD (95% CI)
Retinoid combined with steroids						
Binazzi, 1981[82]	Etretinate + difluocortolone valerate 0.1% ointment	Difluocortolone valerate 0.1% ointment + placebo	30:30	≥ 75% decrease in total score (scale, 0–16)	7/30:4/30	0.36 (0.16 to 0.56)
Christiansen, 1982[83]	Etretinate, 1 mg/kg, + betamethasone valerate 0.1% cream	Etretinate + placebo cream	50:50	Complete or satisfactory remission	29/50:19/50	0.20 (0.01 to 0.39)
		Betamethasone valerate 0.1% cream + placebo	50:46		29/50:14/46	0.28 (0.09 to 0.47)
van der Rhee, 1980[84]	Etretinate, 0.66 mg/kg, + triamcinolone acetonide 0.1% and salicylic acid cream	Etretinate + placebo cream	30:30	Overall improvement	14/30:4/30	0.34 (0.12 to 0.56)
		Triamcinolone acetonide 0.1% and salicylic acid cream + placebo	30:30		14/30:10/30	0.14 (–0.11 to 0.39)
Retinoid combined with calcipotriol						
van de Kerkhof, 1998[62]	Acitretin, 20 mg/day, + calcipotriol	Acitretin, 20 mg/day, + placebo cream	76:59	Clearance or marked improvement	51/76:24/59	0.26 (0.10 to 0.42)

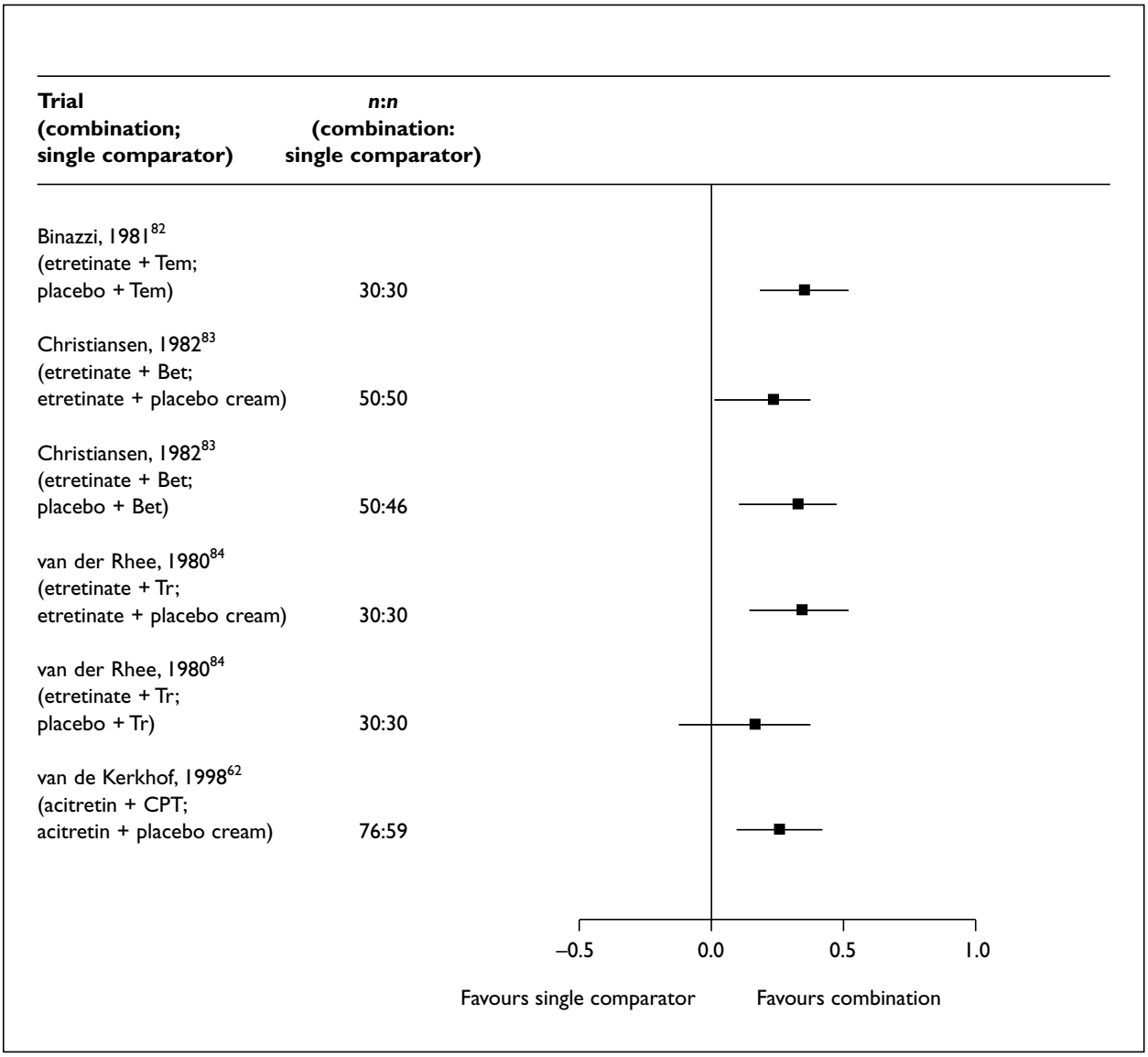

FIGURE 11 *Retinoids and topical agents: RDs (95% CI) (Tem, 0.1% difluocortolone valerate ointment; Bet, 0.1% betamethasone valerate cream b.d.; Tr, 0.1% triamcinolone acetonide and 5% salicylic acid in lanette wax cream; CPT, calcipotriol ointment, 50 µg/g b.d.)*

Chapter 5

Methotrexate

Summary

There is very little robust evidence (no RCT was identified) on either the efficacy of low-dose methotrexate therapy or the precise incidence of side-effects. Although methotrexate has not been formally compared with placebo, there is little doubt that it is effective. How it compares in terms of efficacy, patient acceptability, cost and safety with other established psoriasis treatments is unknown. The success of methotrexate in inducing the remission of psoriasis should be compared formally with cyclosporin, with standard forms of phototherapy, including PUVA, and with intensive outpatient dressing treatment (e.g. the Ingram regimen). Methotrexate would appear to have advantages over both PUVA and cyclosporin in the long-term management of severe psoriasis in that there does not appear to be a time limit beyond which it is unsafe to give methotrexate, as long as liver toxicity does not occur.

Background

Methotrexate has been widely used to treat severe psoriasis since the 1960s.[86] It was the first potent systemic anti-psoriatic agent to be introduced into practice and has continued to play a vital role in the management of severe psoriasis, despite the advent of newer treatments such as photochemotherapy, systemic retinoids and cyclosporin.

Although recognised to be of particular value in the management of acute forms of psoriasis such as acute generalised pustular psoriasis and psoriatic erythroderma, methotrexate has been most widely employed for inducing and then maintaining control of psoriasis in patients with extensive chronic plaque disease that cannot be adequately controlled by topical therapy alone. Methotrexate has found a particular place in the management of patients who also have psoriatic arthritis.[87]

When methotrexate was first introduced for treating psoriasis, it already had an established role in the management of malignant disease and remains one of the most commonly employed anti-metabolites in cancer chemotherapy. Methotrexate is a competitive inhibitor of the enzyme dihydrofolate reductase, thereby decreasing the supply of reduced folate co-factors required for the synthesis of pyrimidine and purine nucleotides in the manufacture of nucleic acid. It has particular effects on rapidly dividing cells. The action of methotrexate in psoriasis was originally thought to be due to the inhibition of epidermal proliferation.[88] However, it has recently been shown that, at concentrations similar to those occurring *in vivo* during low-dose once-weekly therapy, methotrexate has little effect on epidermal cells *in vitro* but significantly inhibits proliferating lymphoid tissue.[89] As a result of an increased understanding of the cellular processes occurring in psoriasis, it is now widely accepted that psoriasis is a T cell-driven disease[90] and that the therapeutic effect of low-dose methotrexate in psoriasis is likely to be due to effects on the immune system rather than on epidermal cells.[91] In contrast, the anti-proliferative actions of methotrexate on epidermal cells and the bone marrow are of more relevance to its acute toxic effects, namely cutaneous ulceration and bone marrow suppression.[91]

Methotrexate can be hazardous if used without due care. Its most important potential side-effect is acute myelosuppression, which is the cause of most of the rare deaths attributable to it when used as a therapy for psoriasis.[91] Methotrexate is eliminated largely via the kidneys, and toxic levels may build up rapidly in the presence of renal impairment. Particular care is required in the elderly, in whom renal function may deteriorate rapidly in response to acute illness; dietary folate deficiency may add to toxicity. Certain drugs, particularly non-steroidal anti-inflammatory agents, aspirin, trimethoprim and sulphonamides, may interfere with methotrexate pharmacokinetics and thus increase the risk of toxicity, particularly in the presence of impaired renal function.[92] Regular monitoring of the full blood count is essential. Folate deficiency should be avoided by the use of oral folic acid supplementation when appropriate.[91]

Long-term methotrexate treatment carries a risk of hepatic fibrosis and cirrhosis, which is related to the dose regimen employed. The original method of administering methotrexate in small daily doses was shown to be much more hepatotoxic than the

same overall amount given as a single weekly dose.[93,94] An alternative regimen that divides the weekly dose into three parts taken at 12-hour intervals over 36 hours is still widely used,[88] although the theoretical basis on which it was devised is now thought unlikely to be valid.[95] Liver toxicity is increased by alcohol abuse, and patients who are unable to restrict alcohol consumption are unsuitable for methotrexate therapy.[91]

Unfortunately, liver toxicity cannot be detected reliably by standard tests of liver function, which may remain normal in the presence of hepatic cirrhosis. The Psoriasis Task Force of the American Academy of Dermatology has recently reiterated its recommendations that liver biopsy should be performed on patients with psoriasis after treatment has been established and thereafter following each cumulative dose of 1.5 g of methotrexate, in practice about every 18 months to 2 years for the average patient.[96] Others have argued that the morbidity and potential hazards of performing regular liver biopsy in patients receiving long-term low-dose methotrexate for psoriasis are difficult to justify when measured against the low yield of information resulting in a change of management.[97] A number of workers have recommended that a serological marker of hepatic fibrosis, the aminoterminal peptide of type III procollagen, may be used to screen for underlying hepatic damage and that liver biopsy may then be reserved for patients with consistently abnormal results.[98,99] Further validation work on these recommendations is currently being undertaken in a UK multicentre HTA study.

At the time of the introduction of methotrexate, not only was this drug already available for treating malignancy, but it was not customary to conduct comparative studies of the efficacy of new therapies. For these reasons, few studies comparing methotrexate with other therapies or with placebo were performed before it was accepted into routine practice.

Although most dermatologists have accepted that methotrexate is highly effective for treating severe psoriasis, there is very little robust evidence that will allow the dermatologist to know how effective it is or how it compares with other therapies. It was initially used in small daily doses, but these were soon replaced by weekly single or divided dose schedules.[88,100] Nyfors and Brodthagen used a methotrexate dose of 25 mg weekly (higher than would now commonly be used for an average patient) and found that 41 of 50 patients (82%) showed a greater than 50% improvement in psoriasis severity.[93] Weinstein and Frost used a weekly triple-dose regimen, dividing the weekly dose into three consecutive 12-hour doses, and found greater than 50% improvement in 20 of 26 patients (77%).[88] Jeffes and Weinstein later claimed that greater than 90% clearance could be achieved in 30–50% of patients treated aggressively.[101] Of 252 patients with psoriasis who were followed for up to 20 years, Zachariae stated that 60% were greatly improved, 30% modestly improved and only 10% not improved by methotrexate.[102] In another retrospective study involving 98 patients with a history of psoriasis who had previously suffered rapid relapse following clearance by the Ingram method (inpatient anthralin and UVB phototherapy), maintenance treatment with methotrexate was commenced during a further course of Ingram therapy; relapse rates were compared with historical controls available for 46 patients in the cohort.[103] Without methotrexate maintenance treatment, psoriasis had begun to reappear within 1 month and had relapsed to pre-treatment severity by 5 months. Methotrexate given at weekly doses averaging 7.5–15.0 mg lengthened these intervals to about 1 year and considerably more than 3 years, respectively.[103]

Search results

A total of 111 citations linking methotrexate with psoriasis were identified. A majority of these addressed the side-effects of methotrexate (particularly on the liver), rather than efficacy. However, 31 citations were reports of the therapeutic use of methotrexate for psoriasis. Titles and abstracts were read by two people independently (CMC and RJGC) to identify possible RCTs. Of the 31 citations, 29 proved to be case series, retrospective reviews or individual case reports, and two appeared to be reports of RCTs. A third RCT was identified from searches for studies of hydroxyurea for psoriasis. All the reports were retrieved and read but failed to fulfil the criteria for inclusion (see appendix 3). No RCT was identified in which standard methods of methotrexate administration for psoriasis were compared either with placebo or with any alternative treatment modality in patients with chronic plaque psoriasis.

Discussion

Methotrexate has been widely used for the treatment of severe psoriasis for over 30 years.

It has been accepted by dermatologists as a highly effective drug and remains central to the management of severe psoriasis throughout the world. With careful selection of patients and meticulous monitoring of therapy, methotrexate also appears to be a safe treatment. Published studies and case series would suggest that it can produce a reduction in disease severity of at least 50% in at least three-quarters of patients treated. The true figures may be greater. With the exception of nausea, methotrexate treatment would appear to have a low incidence of symptomatic side-effects. It offers an advantage over cyclosporin and PUVA therapy in that it seems to be safe to use uninterrupted for many years and even decades. The major long-term concern is the development of hepatic fibrosis or cirrhosis. Newer methods of monitoring for hepatotoxicity, using serological markers of fibrosis, appear to reduce greatly the requirement for liver biopsy and may thus make methotrexate a more attractive option for patients, dermatologists and healthcare providers alike.

Chapter 6

Phototherapy and photochemotherapy

Summary

In all, 51 RCTs were included in this review of phototherapy and photochemotherapy for psoriasis: 22 trials concerned the use of UVA, 21 trials concerned the use of UVB, and five trials involved both UVA and UVB. The remaining three trials used natural sunlight as the UV source. All the trials were primarily concerned with the induction of remission of psoriasis. The trials involved comparisons of phototherapy or photochemotherapy treatment regimens and comparisons of phototherapy or photochemotherapy in combination with retinoids or topical treatments.

The main outcome was treatment success measured by a specified decrease in the PASI score or the extent of body surface area involved or by a global improvement scale. Dichotomous data for effectiveness were analysed using RD. It was not possible to pool any of the data because of the marked heterogeneity. Sources of heterogeneity included the initial severity of disease, phototherapy doses and regimens, success criteria, duration of treatment, the mix of psoriasis subtypes, the mix of skin types and compliance. Because of these factors and the small size of many of the trials, conclusions can be only tentative, at best.

PUVA using oral psoralen (8-MOP, 0.6–1.0 mg/kg) proved to be effective in clearing psoriasis. PUVA using topical psoralen (bath PUVA) was equally effective. UVA alone did not clear psoriasis.

UVB was effective in clearing psoriasis. NBUVB administered three times weekly offers the possibility of clearance with fewer episodes of erythema and may require a lower cumulative dose of UVB.

It is not known how NBUVB or broadband UVB (BBUVB) compares with PUVA. UVB plus UVA may have similar efficacy to PUVA.

PUVA or UVB in combination with retinoids appeared to be more effective than either treatment alone (see chapter 4 for detailed discussion).

There are no evaluable RCTs that compare the effects of adding topical tar to either PUVA or UVB with PUVA, or to UVB alone.

One trial showed that PUVA is as effective as daily dithranol in clearing psoriasis, but there are no trials that evaluate the effects of adding PUVA to dithranol treatment.

Combinations of phototherapy or photochemotherapy with either vitamin D_3 analogues or topical steroids appeared to show that the combinations were superior to each agent used alone.

The main risks of PUVA therapy are photoageing (premature skin ageing) and skin cancer, notably squamous cell carcinoma. As such, it is advisable to limit the number of treatments to less than 250 or a cumulative UVA dose of 1000 joules/cm^2 (J/cm^2). BBUVB radiation does not appear to be associated with the development of skin cancer. There are no long-term studies to assess whether or not NBUVB carries a risk of skin cancer.

Background

Two forms of 'phototherapy' are used in the management of patients with psoriasis.

- Phototherapy entails the use of either BBUVB (290–320 nm) or the more recently introduced NBUVB (311 nm).
- Photochemotherapy entails the use of photosensitising chemicals, such as psoralens, in conjunction with UV radiation, usually long-wavelength UVA (320–400 nm).

The mechanism of action of both UVB and PUVA in treating psoriasis is thought to be immunomodulatory – mainly modulation of the expression of cellular adhesion molecules and induction of T cell apoptosis.[104]

BBUVB phototherapy was first used by Goeckerman[105] in conjunction with crude coal tar, but it later became apparent that UVB given in erythemagenic doses was capable on its own of producing improvement in psoriasis. In recent years, it has been demonstrated that UV wavelengths shorter than 295 nm have no therapeutic effects in psoriasis and indeed that wavelengths between 300 and 313 nm are the most effective in treating

psoriasis. On this basis, new fluorescent bulbs with an emission spectrum of 311–312 nm, so-called 'narrowband' UVB, have been developed. One such bulb is the TL-01 fluorescent lamp (Philips Company, The Netherlands). Undoubtedly, NBUVB phototherapy is a more effective monotherapy for psoriasis than is BBUVB. Treatments are traditionally given 2–3 times weekly until psoriasis is cleared; maintenance treatment, if required, is continued once weekly to maintain clearance. There is conjecture as to whether NBUVB phototherapy is as effective as photochemotherapy. Studies are in progress to ascertain whether this is the case. The benefit of using tar therapy in conjunction with UVB is widely accepted, as is the practice of using other topical therapies such as corticosteroids or vitamin D_3 analogues. The use of UVB phototherapy is undoubtedly associated with an increased incidence of premature skin ageing, although there is still uncertainty as to whether there is an increase in skin carcinogenesis with this particular treatment modality. However, it would be prudent to assume that there is an increased risk and that patients should be counselled and assessed accordingly.

The acronym PUVA is derived from the combination of psoralens, traditionally oral 8-MOP, and exposure to the long-wavelength UVA irradiation. Further experience with photochemotherapy has led to the use of other psoralens and delivery either orally or topically (so-called 'local' or 'bath' PUVA). The basis of photochemotherapy is not new. In ancient Egypt, psoralens belonging to the furocoumarin group were applied topically to the skin prior to natural sun exposure as a treatment for vitiligo.[106] There is evidence that furocoumarins were also taken orally by Egyptians for the same purpose. 8-MOP was successfully isolated in 1948 and was used in the treatment of psoriasis as a topical preparation in combination with UVA in 1973 and orally in 1974.[107,108]

Prior to treatment with PUVA, it is recommended that patients are examined for evidence of photoageing and skin cancer, that any photosensitising drugs are discontinued and that co-existing photodermatoses are excluded.[109] The UVA radiation dose is determined not by an individual's skin type but as a result of testing sensitivity to UVA radiation. The standard regimen employed today is that 8-MOP is taken orally (0.6 mg/kg) 2 hours prior to UVA irradiation. The dose of UVA is increased according to response to therapy and the presence or absence of erythema. In cases of gastrointestinal intolerance to 8-MOP, 5-MOP may be substituted and is taken at a dose of 0.6–1.2 mg/kg 1 hour before irradiation. On treatment days, patients wear UVA-opaque glasses (plastic lenses) and avoid sun exposure. Protective glasses are worn because of a low but probably real risk of PUVA-induced cataract. Courses of treatment usually last for about 24 treatments, with two to three treatments given weekly.

Bath PUVA refers to the practice of immersing the patient in a bath containing a 0.5 mg/l aqueous solution of 8-MOP at a constant temperature of 37.5°C for 20 minutes. Immediately after the bath, the patient is exposed to UVA radiation.[110] Bath PUVA avoids the systemic effects of psoralens, and the photosensitisation is rapidly dissipated. The patient is thus not as restricted as with oral PUVA.

Some centres advocate maintenance treatment with PUVA, but ideally treatment should be stopped after clearance of psoriasis has been achieved. The overriding risk of long-term and cumulative PUVA therapy is skin cancer, most notably squamous cell carcinoma and to a lesser extent basal cell carcinoma.[111] Recently, concerns have been voiced about the development of melanoma as a result of high-dose, long-term PUVA treatment.[112] To attempt to reduce the long-term risks of PUVA, it is recommended that patients: (a) use protective eyewear, (b) in the case of males, cover the genitalia during UVA exposure, (c) use an opaque sunscreen for lips and (d) cover the face, unless it is significantly affected by psoriasis. The British Photodermatology Group recommends that lifetime exposure to PUVA should be limited to less than 1000 J/cm^2 of UVA or 250 treatments.

Search results

A total of 332 citations were identified for psoriasis and PUVA, UVA or UVB. These citations included studies of the therapeutic use of PUVA, UVA or UVB (RCTs, cohort studies, retrospective studies, case reports and small series) together with reviews and studies of biochemical effects of phototherapy. The titles and abstracts were reviewed by two people independently (CMC and CEMG) to identify RCTs, and 96 records appeared to be reports of RCTs. All these reports were retrieved and read. Of these 96 reports, 34 were non-randomised (or partially randomised) studies, and two were animal studies. A further five studies were excluded because they involved non-randomised, left/right comparisons, and four other studies were excluded because their

evaluation depended on the response in target lesions only. As neither of these two latter situations reflects the real-life treatment situation, these studies were not really comparable with the others included in the review, and therefore their exclusion was considered justified. Furthermore, left/right comparison studies do not adequately prevent contamination or systemic effects of UV therapy. In total, 45 reports were excluded from the final list (see appendix 4). Thus, 51 RCTs were available for inclusion in this review.[55,60,61,75–81,113–155]

Characteristics of included studies

The characteristics of the trials are summarised in *Tables 27–32*. These 51 RCTs may be conveniently divided into:

- comparisons of treatment schedules for psoralen photochemotherapy (*Table 27*)
- comparisons of UVB treatment schedules (*Table 28*)
- comparisons of photochemotherapy with other phototherapy treatment schedules (*Table 29*)
- comparisons of phototherapy plus retinoids with phototherapy or retinoids (*Table 30*)
- photochemotherapy trials using sunlight as the UV source (*Table 31*)
- comparisons of phototherapy and/or topical treatment schedules (*Table 32*).

In order to decide whether or not the data from the separate trials could reasonably be pooled statistically, the reports were examined to determine the degree of similarity between them. Of the 51 RCTs, 22 trials concerned the use of UVA, 21 trials concerned the use of UVB, and five trials involved both UVA and UVB. The remaining three trials used natural sunlight as the UV source. There were considerable variations in the initial severity of the disease, phototherapy doses, success criteria and duration of treatment. Other factors that may have contributed to the variability in the results included the mix of patients, both in terms of the type of psoriasis and skin type, and compliance with treatment. Although trials involving patients with chronic plaque psoriasis were selected (and no studies of phototherapy specifically for guttate psoriasis were found), several series contained a number of patients with guttate psoriasis. In none of these trials was randomisation stratified by psoriasis type.

Thirteen of the trials used an objective disease severity criterion for inclusion. All these criteria were threshold values for the percentage of body surface area affected (range, 10–40%). The remainder of the studies gave a description such as 'severe psoriasis', 'widespread psoriasis', 'psoriasis severe enough to require PUVA' or simply 'psoriasis'. Nineteen of the trials used an objective (or quasi-objective) criterion for success, such as a 75% decrease in PASI, modified PASI or global score. The remainder either did not report a success criterion or relied on descriptions such as 'clear', 'complete remission' or 'satisfactory response'.

Phototherapy regimens were described in detail (i.e. dose, frequency and dose adjustments). The duration of treatment was described in weeks or by the number of phototherapy exposures. Trial durations varied from 2 to 10 weeks.

Results

RCTs comparing treatment schedules for psoralen photochemotherapy

RCTs comparing different oral psoralens

Six trials compared different treatment regimens for oral psoralens (*Table 33*). Two of these studies examined differences between the oral psoralen doses used for PUVA. Andrew and colleagues[113] showed that 8-MOP given at a dose of 40 mg was associated with a greater success rate than 8-MOP given at a dose of 10 mg (RD, 0.72; 95% CI, 0.54 to 0.90) and that a lower mean cumulative UV dose was required to achieve success (54.0 J/cm^2 [range, 14.5–115.0 J/cm^2] vs 77.0 J/cm^2 [range, 46.0–113.0 J/cm^2], respectively). Similarly, Tanew and colleagues[115] showed that 5-MOP cleared psoriasis at a significantly lower mean cumulative UVA dose when the oral drug was given at a dose of 1.2 mg/kg (UVA dose ± SD, 53 ± 33 J/cm^2) rather than 0.6 mg/kg (UVA dose, 132 ± 87 J/cm^2).

Three trials compared different psoralens or psoralen formulations. One study compared different formulations of the same psoralen.[114] Liquid 8-MOP was shown to be more effective than crystalline 8-MOP (RD, 0.25; 95% CI, –0.01 to 0.51). There was no significant difference in the total UVA energy requirements for the two groups (68.7 J/cm^2 for liquid psoralen vs 80.8 J/cm^2 for crystalline psoralen).

Two studies compared oral 8-MOP with oral 5-MOP. In the study by Tanew and colleagues,[115] two doses of 5-MOP (0.6 mg/kg and 1.2 mg/kg, as indicated above) were compared with 8-MOP (0.6 mg/kg). They found no difference in the mean cumulative UVA dose (± SD) required to

TABLE 27 *Design of trials comparing psoralen photochemotherapy treatment schedules*

Trial	Intervention	Comparator	Design	*n:n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
UVA combined with oral psoralen						
Andrew, 1981[113]	PUVA three times a week (8-MOP, 40 mg)	PUVA three times a week (8-MOP, 10 mg)	SB, parallel group	26:30	Extensive chronic plaque psoriasis of the trunk and limbs	Major improvement or full remission after 12 treatments See *Notes*
Berg, 1994[116]	PUVA twice a week (5-MOP)	PUVA twice a week (8-MOP)	DB, parallel group	19:19	Medium severe to severe psoriasis	Modified PASI (0–108), "healed or nearly healed"
Collins, 1996[117]	PUVA twice a week, using MPD (8-MOP)	PUVA twice a week, with dose based on skin type (8-MOP)	SB, parallel group	37:37	Chronic plaque psoriasis, ≥ 8% BSA affected	Clearance ± minimal residual activity
Lowe, 1987[114]	PUVA three times a week (liquid 8-MOP)	PUVA three times a week (crystalline 8-MOP)	DB, parallel group	25:22	Plaque, pustular or erythrodermic psoriasis, ≥ 20% BSA affected	Marked improvement or complete clearance after 20 treatments or fewer
Tanew, 1988[115]	PUVA four times a week (5-MOP capsules, 0.6 mg/kg)	PUVA four times a week (8-MOP capsules, 0.6 mg/kg)	NB, parallel group	58:48	Chronic plaque, guttate and seborrhoeic psoriasis See *Notes*	Complete clearance
	PUVA four times a week (5-MOP capsules, 1.2 mg/kg)			63:48		
Buckley, 1995[118]	PUVA three times a week, with dose based on skin type	PUVA twice a week, using MPD	NB, parallel group, 6 weeks	41:42	> 10% BSA affected	Clearance (complete resolution or < 1% BSA affected)
UVA combined with topical psoralen						
Calzavara Pinton, 1997[121]	PUVA four times a week (8-MOP, bath)	PUVA four times a week (5-MOP, bath)	NB, crossover	5:5	Recurrent, widespread	PASI (no threshold reported)

MPD, minimal phototoxic dose

Trial	***Notes***
Andrew, 1981[113]	*Patients were initially randomised to receive 10 or 40 mg of 8-MOP; those receiving 10 mg who did not respond after 12 treatments were then given larger doses (up to 40 mg)*
Tanew, 1988[115]	*Patients with plaque-type psoriasis were treated with RePUVA using etretinate; as these patients were evenly distributed throughout the three groups, this potential confounder was ignored in the analysis*

continued

TABLE 27 contd *Design of trials comparing psoralen photochemotherapy treatment schedules*

Trial	Intervention	Comparator	Design	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
***UVA combined with topical psoralen* contd**						
Collins, 1992[119]	PUVA three times a week (8-MOP, bath)	PUVA three times a week (8-MOP, oral)	SB, parallel group	22:22	≥ 10% BSA affected	Clearance
Turjanmaa, 1985[120]	PUVA three times a week (bath)	PUVA three times a week (oral)	NB, parallel group	50:43	Plaque psoriasis	Excellent or good

TABLE 28 *Design of trials comparing UVB phototherapy treatment schedules*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Dawe, 1998[125]	NBUVB three times a week	NBUVB five times a week	SB, parallel group, left/right, 30 exposures	21:21	Chronic plaque psoriasis	Clearance or minimal residual activity
Hofer, 1998[126]	NBUVB "far"* three to five times a week	NBUVB "near"* three to five times a week	Not reported, parallel group, left/right, 3 weeks	13:13	Plaque/guttate and guttate psoriasis	≥ 75% decease in PASI
Larkö, 1989[122]	NBUVB three to five times a week	UVB three to five times a week	DB, parallel group, left/right, 8 weeks	29:29	Psoriasis (average 57% BSA involved)	Not explicitly reported; group results reported
Storbeck, 1993[124]	NBUVB three to five times a week	UVB three to five times a week	Not reported, parallel group, left/right	23:23	Widespread symmetrical psoriasis	Not reported
Picot, 1992[123]	NBUVB three times a week	UVB three times a week	DB, parallel group, left/right, 10 weeks	21:21	Plaque-type, plaque/guttate and guttate psoriasis	Not explicitly reported; group results reported

* *Hofer* et al.[126] *defined "far" dose as initial treatment with 35% of the minimum erythema dose (MED) and "near" dose as initial treatment with 70% of the MED*

TABLE 29 *Design of trials comparing PUVA with other phototherapy treatment schedules*

Trial	Intervention	Comparator	Design	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Mizuno, 1980[130]	PUVA (topical 8-MOP)	UVA + placebo solution	DB, parallel group	Not extractable (111 patients in total)		
Pai, 1994[129]	PUVA three times a week	UVA three times a week	DB, parallel group,	12:12	Psoriasis affecting ≥ 20% BSA	Not reported
Van Weelden, 1990[127]	PUVA twice a week	NBUVB twice a week	SB, parallel group	10:10	Widespread psoriasis	Overall impression
Van Weelden, 1980[131]	PUVA twice a week	Placebo capsules + UVA + UVB	DB, parallel group	15:15	Severe psoriasis	Not reported
de Berker, 1997[128]	PUVA twice a week	PNBUVB twice a week	SB, parallel group	50:50	Plaque-type psoriasis; patient referred to PUVA clinic	All exposed lesions above knees cleared

TABLE 30 *Design of trials comparing phototherapy with retinoids (including UV versus retinoids and UV plus retinoids versus other treatments)*

Trial	Intervention	Comparator	Design	*n:n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Lauharanta, 1989[77]	Bath PUVA three times a week + acitretin	Bath PUVA three times a week + etretinate	DB, parallel group	17:17	"Widespread plaque-type psoriasis"	≥ 90% decrease in PASI
Lauharanta, 1981[76]	PUVA up to three times a week	Etretinate alone, then etretinate + PUVA	NB, parallel group	20:20	"Severe psoriasis"	≥ 75% decrease in PASI
		Etretinate alone, then PUVA		20:20		
		Etretinate		20:20		
Parker, 1984[75]	PUVA + etretinate	PUVA + placebo	NB, parallel group	15:15	> 20% BSA affected	Clearance (< 2% BSA affected)
Saurat, 1988[78]	PUVA three times a week + etretinate	PUVA three times a week + placebo	DB, parallel group	23:22	Severe psoriasis with > 20% BSA affected, or erythrodermic psoriasis	≥ 75% decrease in PASI
	PUVA three times a week + acitretin			20:22		
Sommerburg, 1993[79]	PUVA three to five times a week + acitretin	PUVA three to five times a week + placebo	DB, parallel group	44:44	"Generalised chronic plaque psoriasis severe enough to require PUVA"	≥ 75% decrease in PSI
Tanew, 1991[80]	PUVA twice a week + acitretin	PUVA twice a week + placebo	DB, parallel group	30:30	"Severe and extensive psoriasis – > 20% BSA"	≥ 90% clearance of psoriasis
Green, 1992[55]	PUVA twice a week + etretinate	NBUVB three times a week + etretinate	Not reported, parallel group	15:15	"Extensive chronic plaque or guttate psoriasis	"Satisfactory response"
		NBUVB three times a week		15:15		
Lowe, 1991[81]	Acitretin + UVB	Placebo + UVB	SB, parallel group	16:18	Moderate–severe psoriasis with > 20% BSA affected	Not reported
Ruzicka, 1990[60]	Acitretin + UVB	Placebo + UVB	DB, parallel group	42:40	Generalised chronic plaque or "exanthematous"-type psoriasis severe enough to require combination treatment	≥ 75% decrease in PASI
Iest, 1989[61]	Acitretin + UVB	Acitretin	Not reported, parallel group	9:9	Chronic plaque psoriasis with ≥ 10% BSA affected	≥ 80% clearance of lesions
		UVB		9:32		

TABLE 31 *Design of trials of psoralens using natural sunlight as the UV source*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Parrish, 1977[155]	Sun + 8-MOP	Sun + placebo	DB, parallel group	6:6	Chronic stable or flaring psoriasis affecting ≥ 10% BSA	
Sehgal, 1981[132]	Sun + 8-MOP	Sun + TMP	Not reported, parallel group, 2–8 weeks	17:23	Psoriasis	≥ 75% improvement
Sadananda Naik, 1981[133]	Sun + psoralen	Sun + placebo	DB, parallel group, 4 weeks	20:20	Not reported	≥ 95% improvement

TMP, trimethylpsoralen

TABLE 32 *Design of trials of combined phototherapy and topical treatment schedules*

Trial	Intervention	Comparator	Design and duration	*n:n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Phototherapy vs dithranol						
Larkö, 1983[134]	UVB three times a week	Dithranol 0.2% (Psoradrate 0.2%)	DB, parallel group, 6 weeks	50:50	Chronic, symmetrical psoriasis	Not reported
		Placebo cream		50:50		
Rogers, 1979[135] and Vella Briffa, 1978[136]	PUVA three times a week See *Notes*	Dithranol daily	NB, parallel group	113:111	Chronic plaque psoriasis	Clearance: plaques flat, and not scaly or erythematous
Treatment schedules involving phototherapy and dithranol						
Brandt, 1989[137]	UVB pre-treatment + dithranol	Dithranol + UVB post-treatment	NB, parallel group	15:15	Psoriasis	Not reported
Christensen, 1989[138]	UVB + micro-encapsulated dithranol 1% See *Notes*	UVB + extemporaneously prepared dithranol 1% See *Notes*	SB, parallel group	37:37	Suitable for day care: psoriasis affecting 5–15% BSA	Severity score < 1 (scale, 0–4)
Morison, 1978[140]	Dithranol daily for 6 weeks, then PUVA twice a week See *Notes*	Dithranol daily and PUVA twice a week See *Notes*	NB, parallel group	19:20	Psoriasis (average BSA, 35%; range, 10–90%)	Clearance: ≤ 1% BSA involved
Paramsothy, 1988[139]	Dithranol + tar + UVB	Dithranol + emulsifying ointment bath	NB, parallel group	27:26	Stable chronic plaque psoriasis requiring inpatient treatment	Clearance: ≤ 3% BSA involved
Storbeck, 1993[124]	NBUVB or BBUVB	NBUVB or BBUVB with dithranol	NB, parallel group, left/right	23:23	Widespread, symmetrical psoriasis	Not reported

Trial	***Notes***
Vella Briffa, 1978[136]	*This reference reports the same patient group as Rogers, 1979,[135] but contains some additional data*
Christensen, 1989[138]	*Micro-encapsulated dithranol 1% (biogram dithranol): dithranol is micro-encapsulated in crystalline monoglycerides, which form multi-lamellar layers around the dithranol particles; the hydrophobic sides of the crystals face the dithranol, and the hydrophilic sides face the aqueous phase* *Extemporaneously prepared dithranol: dithranol, 1 part; sodium lauryl sulphate, 2.5 parts; cetanol, 19 parts; liquid paraffin to 100 parts*
Morison, 1978[140]	*Of the seven groups in the study, only six groups were allocated randomly; the "control" group (receiving PUVA and lubricants alone) comprised "consecutive suitable patients"* *The strength and type of preparation were selected according to site and response (dithranol 0.25–1.00% ointment, dithranol 0.1–0.4% in Lassar's paste or dithranol 0.4% in a pomade base)*

continued

TABLE 32 contd *Design of trials of combined phototherapy and topical treatment schedules*

Trial	Intervention	Comparator	Design and duration	*n:n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
Treatment schedules involving phototherapy and tar						
Menkes, 1985[141]	Suberythematous UVB + tar oil	Maximally erythematous UVB + emollients	NR, parallel group	30:19	Stable plaque-type psoriasis, appropriate for outpatient UVB treatment	Clearance: complete resolution of at least 90% of psoriasis exposed to UVB
Morison, 1978[140]	Tar daily for 6 weeks, then PUVA twice a week	Tar daily + PUVA twice a week	NR, parallel group	2:19	Psoriasis (average BSA, 35%; range, 10–90%)	Clearance: ≤ 1% BSA involved
Williams, 1985[142]	PUVA twice a week	UVB + tar five times a week	NR, parallel group	4:2	Psoriasis affecting ≥ 20% BSA	Considerable improvement/clear, based on 6-point scale
Treatment schedules involving phototherapy and vitamin D_3 analogues						
Aktas, 1995[143]	PUVA + calcipotriol	PUVA + placebo	NR, parallel group	10:10	Chronic plaque psoriasis	Not reported
Bourke, 1997[146]	Calcipotriol, 100 g/week	NBUVB three times a week	NR, parallel group	10:10	Chronic plaque psoriasis	Not reported
	Calcipotriol, 100 g/week, + NBUVB three times a week			10:10		
Frappaz, 1993[144]	PUVA + calcipotriol	PUVA + placebo ointment	DB, parallel group	54:53	Extensive psoriasis affecting 20–50% BSA, for which PUVA is indicated	≥ 75% decrease in PASI
Kragballe, 1990[145]	UVB + calcipotriol	UVB	NB, parallel group, left/right	20:20	Chronic plaque psoriasis	Clear, based on global assessment
Röcken, 1998[149]	Tacalcitol + NBUVB three to five times a week	Tacalcitol	NB, parallel group, left/right	24:24	Plaque stage or guttate-type psoriasis	Not reported
Treatment schedules involving phototherapy and steroids						
Hanke, 1979[153]	PUVA + betamethasone valerate 0.1%	PUVA + eucerin ointment	DB, parallel group, left/right	12:12	Plaque psoriasis affecting ≥ 40% BSA	Clearance, based on 6-point scale See *Notes*

Trial	***Notes***
Hanke, 1979[153]	*Psoriasis cleared in all patients, but combination treatment resulted in faster clearance*

continued

TABLE 32 contd *Design of trials of combined phototherapy and topical treatment schedules*

Trial	Intervention	Comparator	Design and duration	*n:n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion
***Treatment schedules involving phototherapy and steroids* contd**						
Horwitz, 1985[152]	Suberythematous UVB + tar + hydrocortisone valerate cream	Suberythematous UVB + tar + cream vehicle	DB, parallel group	10:9	Widespread, stable plaque-type psoriasis	Clearance: reduction in global severity score to < 10% of VAS
Lärko, 1984[150]	Clobetasol propionate + UVB three times a week	Vehicle + UVB three times a week	DB, parallel group	30:30	Plaque psoriasis	Healed: disappearance of scaling, infiltration and erythema
		Clobetasol propionate	SB, parallel group	30:30		
Lidbrink, 1986[151]	Clobetasol propionate + UVB + dithranol five times a week	UVB + dithranol five times a week	NR, parallel group	26:24	Stable plaque psoriasis of moderate extent	Complete clearance: only slight erythema remaining, ≤ 5 points (scale, 0–30)
Morison, 1978[140]	Fluocinolone acetonide daily for 6 weeks, then PUVA twice a week	Fluocinolone acetonide daily + PUVA twice a week	NR, parallel group	19:19	Psoriasis (average BSA, 35%; range, 10–90%)	Clearance: ≤ 1% BSA involved
Treatment schedule involving phototherapy and fish oil						
Gupta, 1989[154]	UVB twice a week + fish oil capsules b.d.	UVB twice a week + placebo capsules b.d.	DB, parallel group	10:10	Stable psoriasis vulgaris affecting ≥ 10% BSA	Not reported

VAS, visual analogue scale

achieve clearance between 8-MOP (45 ± 32 J/cm^2) and high-dose 5-MOP given at 1.2 mg/kg (53 ± 33 J/cm^2). Berg and Ros,[116] on the other hand, observed lower success rates at both 6 and 9 weeks with 5-MOP (1.2 mg/kg) than with 8-MOP (0.6 mg/kg). The 8-MOP group required a significantly lower UV dose (155 vs 187 J/cm^2; $p < 0.05$) and cleared psoriasis significantly more rapidly (61 days vs 68 days; $p < 0.05$). The results may be partially explained by slow absorption of the 5-MOP, which appeared not to reach peak plasma levels until 3 hours after ingestion, although UVA radiation was administered at 2 hours. Side-effects (severe erythema, pruritus and nausea) were reported in 18 patients (38%) receiving 8-MOP but in only four patients (6%) receiving high-dose 5-MOP and in no patients receiving low-dose 5-MOP.[115] Tanning started earlier with 5-MOP and developed more rapidly than with 8-MOP.

RCTs comparing different UVA schedules

Two trials compared the effects of a minimal phototoxic dose (MPD) of UVA with a dose based on skin type. Collins and colleagues[117] reported no difference in the success rates (RD, 0.03; 95% CI, –0.14 to 0.20). However, the MPD group required fewer exposures (11 vs 14) but a greater cumulative UVA dose (62.9 J/cm^2 vs 39.5 J/cm^2). Buckley and colleagues[118] also found no difference in success rates (RD, –0.03; 95% CI, –0.18 to 0.12). They showed that the MPD group took significantly longer to clear psoriasis (50.0 days [95% CI, 43.0 to 66.0 days] vs 41.0 days [95% CI, 36.0 to 50.0 days]; $p < 0.05$) and required a higher median cumulative UVA dose (78.5 J/cm^2 [95% CI, 59.5 to 113.0 J/cm^2] vs 66.5 J/cm^2 [95% CI, 44.0 to 90.0 J/cm^2]), although this latter difference did not reach statistical significance. Skin types I and II (fair, easily burnt and poorly tanning skin) required significantly higher cumulative UVA doses using the MPD method than with the method based on skin type (70.0 J/cm^2 [95% CI, 55.5 to 112.5 J/cm^2] vs 55.8 J/cm^2 [95% CI, 36.5 to 71.5 J/cm^2]; $p < 0.05$).

RCTs involving topical psoralens

Three trials were concerned with topical psoralens. Two trials compared bath PUVA with oral PUVA. Collins and Rogers[119] showed no difference in success rates between bath (8-MOP) and oral (8-MOP) PUVA (RD, 0.00; 95% CI, –0.28 to 0.28) but a fourfold difference in mean cumulative UVA dose ± SD (14.5 ± 9.8 J/cm^2 for bath PUVA and 60.1 ± 25.4 J/cm^2 for oral PUVA). Similarly, Turjanmaa and colleagues[120] compared trioxsalen bath PUVA with oral 8-MOP and showed no difference in success rates (RD, –0.02; 95% CI, –0.17 to 0.13) but a similar reduction in mean cumulative UVA dose required for clearance (23.5 J/cm^2 [range, 0.7–143.0 J/cm^2] vs 131.1 J/cm^2 [range, 7.5–543.0 J/cm^2]).

Calzavara Pinton and colleagues[121] found little difference in efficacy between topical 5-MOP and topical 8-MOP. All patients in both groups were treated until their psoriasis had cleared. There was no difference in mean total UVA dose ± SD (56.8 ± 39.2 J/cm^2 vs 59.1 ± 27.9 J/cm^2, respectively) or number of exposures (20.0 ± 5.7 vs 21.6 ± 4.7, respectively).

RCTs comparing UVB phototherapy treatment schedules

Table 34 shows the results of the five trials that compared UVB treatment schedules. Larkö,[122] Picot and co-workers,[123] and Storbeck and colleagues[124] compared NBUVB with conventional broadband (BBUVB) in left/right randomised studies. From the data reported, it was not possible to calculate response rates in the two groups (sides). In the Larkö study,[122] both sides improved and no differences were recorded in symptom scores (erythema, infiltration, desquamation and itching). The low power of the lamps used by this group meant that radiation times were on average 1.74 times longer than with BBUVB, but the average UV energy required was considerably lower than with BBUVB (0.83 J/cm^2 for NBUVB and 4.80 J/cm^2 for BBUVB). Storbeck and colleagues[124] compared NBUVB and BBUVB in a left/right comparison but also allocated 13 of 23 patients to receive dithranol treatment. NBUVB was reported to be more effective. The mean cumulative UVB doses ± SD were 14.68 ± 9.84 J/cm^2 (BBUVB) and 1.43 ± 1.13 J/cm^2 (NBUVB). Picot and co-workers[123] reported average reductions in PASI score of 78.5% (NBUVB) and 73.9% (BBUVB). These differences were statistically significant ($p < 0.01$). In this study, the mean cumulative UV doses were 15.1 ± 3.8 J/cm^2 (NBUVB) and 7.6 ± 4.2 J/cm^2 (BBUVB). The authors suggested that this difference was due to the rarity and mildness of episodes of erythema caused by TL-01 lamps (NBUVB), allowing steady increases in UV dose. Their results contrast with those of the other two studies.

Two additional studies compared different regimens of NBUVB phototherapy. Dawe and colleagues[125] compared thrice weekly

NBUVB with a five-times-weekly regimen. Psoriasis cleared more quickly with the five-times-weekly regimen, but this success was achieved at the expense of a higher UVB dose and more treatments. Expressed in multiples of the individuals' minimum erythema doses (MEDs), the five-times-weekly sides required a median UVB dose of 94 J/cm^2 (range, 27–164 J/cm^2) compared with 64 J/cm^2 (range, 23–125 J/cm^2) for the three-times-weekly sides. Hofer and colleagues[126] compared NBUVB regimens of different intensity (starting doses of 35% MED vs 70% MED). After three weeks of treatment, there was no difference in success rate (RD, –0.23; 95% CI, –0.58 to 0.12). The group that had started with low-intensity radiation required a median of 16 treatments and received a total cumulative UV dose of 9.10 J/cm^2 (range, 6.28–24.32 J/cm^2) compared with 14.00 J/cm^2 (range, 7.29–21.7 J/cm^2) for the group that had received the high-intensity starting dose.

RCTs comparing PUVA with other phototherapy schedules

Five trials compared PUVA with other phototherapy schedules (*Table 35*). Van Weelden and co-workers[127] compared oral 8-MOP PUVA with NBUVB, and de Berker and colleagues[128] compared oral PUVA with psoralen plus NBUVB (PNBUVB). Van Weelden compared the therapeutic effectiveness of the two treatments, by means of "overall impression", in a left/right comparison in ten patients. Seven patients preferred NBUVB, and three preferred PUVA. Neither total UV doses nor the number of exposures were reported. de Berker and colleagues[128] compared PUVA with PNBUVB in 100 patients. There was no difference in success rates (RD, –0.12; 95% CI, –0.28 to 0.04) or the number of exposures required for clearance, but the UVA group received a median cumulative dose of 72.1 J/cm^2 compared with 19.1 J/cm^2 for the UVB group.

Two trials compared PUVA (using topical 8-MOP) with placebo. Pai and Srinivas[129] reported a success RD of 0.67 (95% CI, 0.38 to 0.96), achieved using a "bathing suit" delivery system. Mizuno[130] compared PUVA, using topical 8-MOP lotion, with UVA and a placebo solution, but the results were not extractable.

Van Weelden and colleagues[131] compared oral 8-MOP PUVA with UVB plus UVA given with placebo capsules. There was no difference in the mean number of exposures (± SEM) required to achieve 80% clearance (25 ± 5 exposures for PUVA and 28 ± 6 exposures for placebo plus UVA–UVB). The placebo plus UVA–UVB group received an average final dose of 2416 ± 693 mJ/cm^2 of UVB. The mean final doses of UVA were similar (14.4 ± 1.6 J/cm^2 for the PUVA group vs 13.2 ± 3.8 J/cm^2 for the placebo plus UVA–UVB group). The authors concluded that UVB plus UVA phototherapy was as effective as oral PUVA. It is not possible to determine how either of these schedules compares with BBUVB alone.

RCTs comparing phototherapy plus retinoids with phototherapy or retinoids

Table 36 summarises the results of trials comparing phototherapy and retinoids with either phototherapy or retinoids. These treatments are described in detail in chapter 4.

RCTs comparing photochemotherapy using sunlight as the UV source

Three trials used natural sunlight as the UV light source (*Table 37*). None of the trials compared the effects of natural sunlight with artificial radiation. Sehgal and Parikh[132] showed that 8-MOP and trimethylpsoralen were equally effective, although neither was particularly efficacious. Sadananda Naik and co-workers[133] showed that the combination of natural sunlight and psoralen (unspecified) was considerably more efficacious for clearing psoriasis than sunlight alone.

RCTs comparing phototherapy and/or topical treatment schedules

Trials in which phototherapy was compared with various forms of topical therapy or combined topical and phototherapy are shown in *Table 38*.

Phototherapy versus dithranol

Two trials compared phototherapy with dithranol. Larkö[134] compared a special formulation of dithranol (Psoradrate®, AB Leo Rhodia, Sweden) with UVB. Unfortunately, success rates were not reported.

Rogers and colleagues[135] and Vella Briffa and colleagues[136] reported different aspects of the same trial comparing PUVA with a standard dithranol regimen. The difference in success rates was not significant, but the time (± SEM) required for clearance was significantly greater in the PUVA-treated group (34.4 ± 1.8 days) compared with the dithranol-treated group (20.4 ± 0.9 days).

Treatment schedules involving phototherapy and dithranol

Five trials compared different combinations of phototherapy with dithranol. Three of these trials concerned combinations with UVB, and one trial concerned PUVA. Brandt[137] undertook a left/right trial of 3% dithranol sticks compared with 0.5–1.0% dithranol in white soft paraffin. Treatment was combined with either suberythematous UVB starting before dithranol treatment or minimally erythematous UVB starting 3 days after dithranol treatment. There was no difference in response to the two dithranol preparations or in the cumulative UVB doses. The time taken to achieve clearance was, however, shorter in the suberythematous UVB group (4.9 weeks) than in the minimally erythematous UVB group (6.2 weeks). Christensen and colleagues[138] compared the combination of UVB with either micro-encapsulated 1% dithranol or extemporaneously prepared 1% dithranol in a left/right, within-patient trial. There was no difference between the treatments, with both clearing psoriasis in 21 of 37 patients in a period of 2–6 weeks. Paramsothy and colleagues[139] compared short-contact dithranol in combination with tar and UVB versus short-contact dithranol in combination with an emulsifying ointment bath. There was no difference in success rates, but UVB treatment appeared to postpone relapse (10.6 weeks without UVB vs 18.9 weeks with UVB; $p < 0.05$). Morison and colleagues[140] compared concurrent PUVA and dithranol with PUVA preceded by 6 weeks of dithranol treatment. Although there was no difference in success rates, the concurrent treatment cleared psoriasis in 60 days compared with 108 days. The corresponding cumulative UVA doses were 12 J/cm^2 (range, 4–35 J/cm^2) compared with 13 J/cm^2 (range 5–27 J/cm^2).

Treatment schedules involving phototherapy and tar

Three trials compared phototherapy treatment schedules with and without tar. Menkes and colleagues[141] compared suberythematous UVB in combination with tar oil versus maximally erythematous UVB and emollients. There was no difference in success rates, but the cumulative UV dose required for clearance was significantly lower in patients treated with tar oil (2.53 vs 4.57 J/cm^2; $p < 0.05$). Morison and colleagues[140] compared concurrent PUVA and tar with PUVA preceded by 6 weeks of tar treatment. As only two patients were entered into the sequential arm of the trial, it is difficult to draw conclusions from this study. The same problem applies to the Williams study[142] comparing PUVA with a UVB and tar combination.

Treatment schedules involving phototherapy and vitamin D_3 analogues

Seven trials compared combinations of phototherapy and vitamin D_3 analogues with phototherapy alone or vitamin D_3 analogue alone.

Two of these trials compared the combination of PUVA and calcipotriol with PUVA and placebo cream. Aktas and colleagues[143] reported no difference between the two treatments, but Frappaz and Thivolet[144] showed a success RD of 0.19 (95% CI, 0.01 to 0.37). In this trial, the cumulative UVA dose was significantly lower in the PUVA plus calcipotriol group (30 vs 57 J/cm^2; $p = 0.021$).

Two trials compared combinations of BBUVB or NBUVB phototherapy and calcipotriol with phototherapy alone.[145,146] Although success rates could not be extracted from their trial, Bourke and colleagues[146] reported a significantly greater fall in PASI in the group receiving combination treatment than in the group receiving UVB alone. The trial reported by Kragballe[145] did not demonstrate a success RD between the two treatments (RD, 0.20; 95% CI, –0.06 to 0.46).

Three trials[146–148] compared combinations of calcipotriol and either BBUVB or NBUVB with calcipotriol alone. In each trial, the combination was superior to treatment with calcipotriol alone.

Röcken and colleagues[149] compared the combination of tacalcitol and NBUVB with tacalcitol alone. Treatment success rates could not be extracted from this trial, but the authors reported a significantly greater fall in the mean severity score for the combination treatment group after 3 weeks ($p < 0.001$).

Treatment schedules involving phototherapy and steroids

Five trials compared combinations of phototherapy and topical steroids with a variety of comparators. Three of these trials concerned combinations with UVB phototherapy, and two involved PUVA. Larkö and colleagues[150] compared the combination of UVB and clobetasol propionate with each treatment alone. The success RDs did not differ between the three treatments. Lidbrink and colleagues[151] compared a UVB–dithranol–steroid combination with the UVB–dithranol combination. Although there was no difference in treatment success rates, the time to healing was significantly faster in the steroid-treated group (2.5 vs

4.0 weeks; $p < 0.05$). Horwitz and colleagues[152] examined the effects of the addition of steroid (hydrocortisone valerate) to a combination of suberythematous UVB and tar. There was no difference in success rates, and the addition of steroid cream did not reduce the number of treatments required for clearing. The average duration of remission was significantly shorter for the steroid-treated group (5.9 weeks) compared with the control group (17.9 weeks). Hanke and colleagues[153] examined the effects of the addition of betamethasone valerate to PUVA treatment. There was no difference in success rates, but the combination took effect more quickly and required a lower cumulative UV dose than PUVA alone (69.96 J/cm^2 [range, 26.50–171.50 J/cm^2] vs 133.71 J/cm^2 [range, 44.50–284.00 J/cm^2]). Morison and colleagues[140] compared concurrent PUVA and topical steroid with PUVA preceded by 6 weeks of steroid treatment. There was no difference in success rates or in the cumulative UVA doses required for clearance (11 J/cm^2 [range, 3–25 J/cm^2] for PUVA and topical steroid vs 12 J/cm^2 [range, 0–18 J/cm^2] for PUVA preceded by topical steroid), although the sequential treatment took longer to clear psoriasis (108 days vs 59 days).

Treatment schedules involving phototherapy and fish oil

Gupta and colleagues[154] examined the effects of the addition of oral fish oil to low-dose UVB phototherapy. Treatment success rates could not be extracted from this trial.

Discussion

The introduction of PUVA treatment in the early 1970s was one of the major advances in therapy for psoriasis. A quarter of a century later, PUVA still holds an important place in the armamentarium for severe disease. Oral psoralen PUVA is somewhat inconvenient for patients because it necessitates sun avoidance and the wearing of protective spectacles on the day of treatment, coupled with the occasional nausea associated with the oral psoralens. Bath PUVA is a convenient alternative and is popular with patients because the aforementioned inconveniences are obviated. Although PUVA is undoubtedly effective, the major concern surrounding its use, particularly in the long term, is the increased incidence of skin cancer, namely squamous cell carcinoma. Guidelines decree that the maximum cumulative UVA dose should not exceed 1000 J/cm^2.

NBUVB is a relatively new innovation and is effective as monotherapy. Its efficacy compared with PUVA is unknown, but clinicians believe it is close to PUVA in this regard. Patients prefer NBUVB because treatment involves no accoutrements such as pills or baths. However, only long-term surveillance will determine whether the risk of skin cancer is less with NBUVB. Comparative studies of PUVA against NBUVB are undoubtedly needed.

The combination of systemic retinoids (i.e. acitretin or etretinate) with PUVA reduces the cumulative dose of PUVA required for clearance and may slow the development of skin cancers. Both PUVA and UVB in combination with topical preparations, such as corticosteroids and vitamin D_3 analogues, are more effective than either alone. Indeed, the use of phototherapy in this way is more reflective of 'real-life' clinical practice as opposed to the somewhat contrived atmosphere of clinical trials.

Overall, photochemotherapy and phototherapy have an important place in the management of severe psoriasis and are an integral part of any dermatology department day-treatment unit. Vigilance is required to ration the use of these therapies, particularly PUVA, as the combination of efficacy and acceptance are strong drivers of patient choice.

TABLE 33 *Treatment success RDs: comparison of treatment schedules for psoralen photochemotherapy*

Trial	Intervention	Comparator	*n*:*n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
UVA combined with oral psoralen						
Andrew, 1981[113]	PUVA three times a week (8-MOP, 40 mg)	PUVA three times a week (8-MOP, 10 mg)	26:30	Major improvement or full remission after 12 treatments See *Notes*	24/26:6/30	0.72 (0.54 to 0.90)
Berg, 1994[116]	PUVA twice a week (5-MOP)	PUVA twice a week (8-MOP)	19:19	Modified PASI (0–108), "healed or nearly healed"	Extracted results: 6/19:12/19 (at 6 weeks) 10/19:14/19 (at 9 weeks)	 –0.31 (–0.58 to –0.04) –0.21 (–0.48 to 0.06)
Collins, 1996[117]	PUVA twice a week, using MPD (8-MOP)	PUVA twice a week, with dose based on skin type (8-MOP)	37:37	Clearance ± minimal residual activity	31/37:30/37	0.03 (–0.14 to 0.20)
Lowe, 1987[114]	PUVA three times a week (liquid 8-MOP)	PUVA three times a week (crystalline 8-MOP)	25:22	Marked improvement or complete clearing after 20 treatments or fewer	20/25:12/22	0.25 (–0.01 to 0.51)
Tanew, 1988[115]	PUVA four times a week (5-MOP capsules, 0.6 mg/kg)	PUVA four times a week (8-MOP capsules, 0.6 mg/kg)	58:48	Complete clearance	55/58:48/48	–0.05 (–0.11 to 0.01)
	PUVA four times a week (5-MOP capsules, 1.2 mg/kg)		63:48		63/63:48/48	0.00 (0.00 to 0.00)
Buckley, 1995[118]	PUVA three times a week, with dose based on skin type	PUVA twice a week, using MPD	41:42	Clearance (complete resolution or < 1% BSA affected)	35/37:37/38	–0.03 (–0.18 to 0.12)
UVA combined with topical psoralen						
Calzavara Pinton, 1997[121]	PUVA four times a week (8-MOP, bath)	PUVA four times a week (5-MOP, bath)	5:5	PASI (no threshold reported)	Not extractable	
Collins, 1992[119]	PUVA three times a week (8-MOP, bath)	PUVA three times a week (8-MOP, oral)	22:22	Clearance	14/22:14/22	0.00 (–0.28 to 0.28)
Turjanmaa, 1985[120]	PUVA three times a week (bath)	PUVA three times a week (oral)	50:43	Excellent or good	42/50:37/43	–0.02 (–0.17 to 0.13)

Trial	***Notes***
Andrew, 1981[113]	*Patients were initially randomised to receive 10 or 40 mg of 8-MOP; those receiving 10 mg who did not respond after 12 treatments were then given larger doses (up to 40 mg)*

TABLE 34 *Treatment success RDs: trials comparing UVB phototherapy treatment schedules*

Trial	Intervention	Comparator	*n:n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Dawe, 1998[125]	NBUVB three times a week	NBUVB five times a week	21:21	Clearance or minimal residual activity	Not extractable	
Hofer, 1998[126]	NBUVB "far" three to five times a week	NBUVB "near" three to five times a week	13:13	≥ 75% decease in PASI	3/13:6/13	–0.23 (–0.58 to 0.12)
Larkö, 1989[122]	NBUVB three to five times a week	BBUVB three to five times a week	29:29	Not explicitly reported; group results reported	Not extractable	
Storbeck, 1993[124]	NBUVB three to five times a week	BBUVB three to five times a week	23:23	Not reported	Not extractable	
Picot, 1992[123]	NBUVB three times a week	BBUVB three times a week	21:21	Not explicitly reported; group results reported	Not extractable	

TABLE 35 *Treatment success RDs: trials comparing PUVA with other phototherapy schedules*

Trial	Intervention	Comparator	*n:n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Mizuno, 1980[130]	PUVA (topical 8-MOP)	UVA + placebo solution	Not extractable (111 patients in total)			
Pai, 1994[129]	PUVA three times a week	UVA three times a week	12:12	Not reported	9/12:1/12	0.67 (0.38 to 0.96)
Van Weelden, 1990[127]	PUVA twice a week	NBUVB twice a week	10:10	Overall impression	Not extractable	
Van Weelden, 1980[131]	PUVA twice a week	Placebo capsules + UVA + UVB	15:15	Not reported	Not extractable	
de Berker, 1997[128]	PUVA twice a week	PNBUVB twice a week	50:50	All exposed lesions above knees cleared	37/50:43/50	–0.12 (–0.28 to 0.04)

TABLE 36 *Treatment success RDs: trials comparing phototherapy with retinoids (including UV versus retinoids and UV plus retinoids versus other treatments)*

Trial	Intervention	Comparator	*n:n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Lauharanta, 1989[77]	Bath PUVA three times a week + acitretin	Bath PUVA three times a week + etretinate	17:17	≥ 90% decrease in PASI	17/17:17/17	
Lauharanta, 1981[76]	PUVA up to three times a week	Etretinate alone, then etretinate + PUVA	20:20	≥ 75% decrease in PASI	16/20:16/20	0.00 (–0.25 to 0.25)
		Etretinate alone, then PUVA	20:20			
		Etretinate	20:20			
Parker, 1984[75]	PUVA + etretinate	PUVA + placebo	15:15	Clearance (< 2% BSA affected)	14/15:9/15	0.33 (0.05 to 0.61)
Saurat, 1988[78]	PUVA three times a week + etretinate	PUVA three times a week + placebo	23:22	≥ 75% decrease in PASI	16/23:16/22	0.12 (–0.12 to 0.36)
	PUVA three times a week + acitretin		20:22		17/20:16/22	0.15 (–0.10 to 0.40)
Sommerburg, 1993[79]	PUVA three to five times a week + acitretin	PUVA three to five times a week + placebo	44:44	≥ 75% decrease in PSI	28/44:19/44	0.20 (–0.01 to 0.41)
Tanew, 1991[80]	PUVA twice a week + acitretin	PUVA twice a week + placebo	30:30	≥ 90% clearance of psoriasis	22/30:20/30	0.06 (–0.17 to 0.29)
Green, 1992[55]	PUVA twice a week + etretinate	NBUVB three times a week + etretinate	15:15	"Satisfactory response"	15/15:12/15	0.07 (–0.06 to 0.20)
		NBUVB three times a week	15:15		15/15:14/15	0.20 (0.00 to 0.40)
Lowe, 1991[81]	Acitretin + UVB	Placebo + UVB	16:18	Not reported	Not extractable	
Ruzicka, 1990[60]	Acitretin + UVB	Placebo + UVB	42:40	≥ 75% decrease in PASI	24/42:9/40	0.34 (0.14 to 0.54)
Iest, 1989[61]	Acitretin + UVB	Acitretin	9:9	≥ 80% clearance of lesions	8/9:2/9	0.67 (0.33 to 1.01)
		UVB	9:32		8/9:20/32	0.26 (0.00 to 0.52)

TABLE 37 *Treatment success RDs: trials of psoralens using natural sunlight as the UV source*

Trial	Intervention	Comparator	*n:n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Parrish, 1977[155]	Sun + 8-MOP	Sun + placebo	6:6			
Sehgal, 1981[132]	Sun + 8-MOP	Sun + TMP	17:23	≥ 75% improvement	6/17:6/23	0.09 (–0.02 to 0.38)
Sadananda Naik, 1981[133]	Sun + psoralen	Sun + placebo	20:20	≥ 95% improvement	12/20:0/20	0.60 (0.39 to 0.81)

TABLE 38 *Treatment success RDs: trials of combined phototherapy and topical treatment schedules*

Trial	Intervention	Comparator	*n:n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Phototherapy vs dithranol						
Larkö, 1983[134]	UVB three times a week	Dithranol 0.2% (Psoradrate 0.2%)	50:50	Not reported	Not extractable	
		Placebo cream	50:50			
Rogers, 1979[135] and Vella Briffa, 1978[136]	PUVA three times a week	Dithranol daily	113:111	Clearance: plaques flat, and not scaly or erythematous	103/113:91/111	0.09 (0.00 to 0.18)
Treatment schedules involving phototherapy and dithranol						
Brandt, 1989[137]	UVB pre-treatment + dithranol	Dithranol + UVB post-treatment	15:15	Not reported	Not extractable	
Christensen, 1989[138]	UVB + micro-encapsulated dithranol 1%	UVB + extemporaneously prepared dithranol 1%	37:37	Severity score < 1 (scale, 0–4)	21/37:21/37	0.00 (–0.23 to 0.23)
Morison, 1978[140]	Dithranol daily for 6 weeks, then PUVA twice a week	Dithranol daily and PUVA twice a week	19:20	Clearance: ≤ 1% BSA involved	16/19:19/20	–0.11 (–0.30 to 0.08)
Paramsothy, 1988[139]	Dithranol + tar + UVB	Dithranol + emulsifying ointment bath	27:26	Clearance: ≤ 3% BSA involved	20/27:16/26	0.12 (–0.13 to 0.37)
Storbeck, 1993[124]	NBUVB or BBUVB	NBUVB or BBUVB with dithranol	23:23	Not reported	Not extractable	
Treatment schedules involving phototherapy and tar						
Menkes, 1985[141]	Suberythematous UVB + tar oil	Maximally erythematous UVB + emollients	30:19	Clearance: complete resolution of at least 90% of psoriasis exposed to UVB	19/30:14/19	–0.11 (–0.37 to 0.15)
Morison, 1978[140]	Tar daily for 6 weeks, then PUVA twice a week	Tar daily + PUVA twice a week	2:19	Clearance: ≤ 1% BSA involved	2/2:16/19	0.16 (0.00 to 0.32)
Williams, 1985[142]	PUVA twice a week	UVB + tar five times a week	4:2	Considerable improvement/ clear, based on 6-point scale	2/4:0/2	0.50 (0.01 to 0.99)
Treatment schedules involving phototherapy and vitamin D_3 analogues						
Aktas, 1995[143]	PUVA + calcipotriol	PUVA + placebo	10:10	Not reported	Not extractable	
Bourke, 1997[146]	Calcipotriol, 100 g/week	NBUVB three times a week	10:10	Not reported	Not extractable	
	Calcipotriol, 100 g/week, + NBUVB three times a week		10:10			

continued

TABLE 38 contd *Treatment success RDs: trials of combined phototherapy and topical treatment schedules*

Trial	Intervention	Comparator	*n*:*n* (intervention: comparator)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
***Treatment schedules involving phototherapy and vitamin D_3 analogues* contd**						
Frappaz, 1993[144]	PUVA + calcipotriol	PUVA + placebo ointment	54:53	≥ 75% decrease in PASI	40/54:29/53	0.19 (0.01 to 0.37)
Kragballe, 1990[145]	UVB + calcipotriol	UVB	20:20	Clear, based on global assessment	7/20:3/20	0.20 (–0.06 to 0.46)
Röcken, 1998[149]	Tacalcitol + NBUVB three to five times a week	Tacalcitol	24:24	Not reported	Not extractable	
Treatment schedules involving phototherapy and steroids						
Hanke, 1979[153]	PUVA + betamethasone valerate 0.1%	PUVA + eucerin ointment	12:12	Clearance, based on 6-point scale	12/12:12/12 See *Notes*	
Horwitz, 1985[152]	Suberythematous UVB + tar + hydrocortisone valerate cream	Suberythematous UVB + tar + cream vehicle	10:9	Clearance: reduction in global severity score to < 10% of VAS	3/10:1/9	0.19 (–0.16 to 0.54)
Lärko, 1984[150]	Clobetasol propionate + UVB three times a week	Vehicle + UVB three times a week	30:30	Healed: disappearance of scaling, infiltration and erythema	18/30:20/30	–0.07 (–0.31 to 0.17)
		Clobetasol propionate	30:30		18/30:13/30	0.17 (–0.08 to 0.42)
Lidbrink, 1986[151]	Clobetasol propionate + UVB + dithranol five times a week	UVB + dithranol five times a week	26:24	Complete clearance: only slight erythema remaining, ≤ 5 points (scale, 0–30)	18/26:15/24	0.06 (–0.20 to 0.32)
Morison, 1978[140]	Fluocinolone acetonide daily for 6 weeks, then PUVA twice a week	Fluocinolone acetonide daily + PUVA twice a week	19:19	Clearance: ≤ 1% BSA involved	17/19:19/19	–0.11 (–0.25 to 0.03)
Treatment schedule involving phototherapy and fish oil						
Gupta, 1989[154]	UVB twice a week + fish oil capsules b.d.	UVB twice a week + placebo capsules b.d.	10:10	Not reported	Not extractable	

Trial	*Notes*
Hanke, 1979[153]	*Psoriasis cleared in all patients, but combination treatment resulted in faster clearance*

Chapter 7

Hydroxyurea, fumarates, azathioprine and sulphasalazine

Hydroxyurea

Summary

Hydroxyurea is a commonly used systemic therapy for severe psoriasis, often employed as a substitute when cyclosporin and methotrexate are contraindicated. There is little robust evidence (i.e. only one relatively poor RCT) showing that hydroxyurea is an effective treatment for psoriasis. Side-effects include bone marrow suppression and teratogenicity. There is a need for RCTs of hydroxyurea compared with placebo.

Background

Hydroxyurea is an anti-metabolite that has been used principally for the treatment of malignant disease, in particular chronic myeloid leukaemia and carcinoma of the cervix uteri. With the realisation in the 1960s of the hepatotoxic potential of methotrexate, dermatologists began to look for alternative systemic agents. Hydroxyurea was first recommended for psoriasis by Yarbro in 1969.[156] Since then, several small studies and retrospective case series of its use in a total of about 300 patients have been published. The use of hydroxyurea in psoriasis has recently been reviewed.[157]

The active drug, which is converted *in vivo* from its parent, is a free radical nitroxide that selectively inhibits DNA synthesis in proliferating cells. It is not known whether its effects on psoriasis are due to the inhibition of epidermal proliferation or effects on proliferating lymphoid cells.

Bone marrow suppression is a common side-effect of treatment with hydroxyurea, and indeed some degree of leucopenia is seen in a majority of treated patients. The effect is dose related and reversible. Anaemia and thrombocytopenia are less frequent adverse effects. Overall, however, dose reduction or temporary cessation of treatment is required in up to one-third of patients on long-term therapy because of haematological abnormalities.[157] Macrocytosis is an almost universal side-effect. Careful monitoring for haematological toxicity is required in all patients.

Although the use of hydroxyurea in treating psoriasis has not been reported to be associated with the development of malignancy, an increased risk cannot be excluded.[157] Other side-effects of low-dose hydroxyurea, in particular on the liver and kidney, appear to be rare. This fact has been seen as an advantage for patients in whom drugs such as cyclosporin or methotrexate may be contraindicated. Because it is teratogenic, hydroxyurea must be avoided during pregnancy.

In the three largest case series of patients with psoriasis treated with hydroxyurea[158–160] (between them accounting for about three-quarters of published cases), the reported satisfactory response rates have ranged from 45% to 80%. Its use has generally been reserved for patients who have either failed to respond or have had contraindications to the use of other systemic agents, such as methotrexate or cyclosporin. Hydroxyurea may be effective when such drugs have failed, but it would seem overall to be a less potent anti-psoriatic agent than these drugs. Some dermatologists have therefore advocated using hydroxyurea in conjunction with other systemic agents, including methotrexate,[161] cyclosporin,[162] etretinate[163] and acitretin.[164]

Search results

Six citations linking hydroxyurea with psoriasis were identified by our standard search strategy. Titles and abstracts were read by two people individually to identify possible RCTs. Four citations appeared to be reports of the therapeutic use of hydroxyurea for psoriasis. None of these appeared to be RCTs. A broader search was therefore undertaken to identify all records containing the terms 'hydroxyurea' and 'psoria*' that were cited in the Cochrane Controlled Trials Register 1999, MEDLINE from 1966 to 1999 and EMBASE from 1980 to 1999. This search yielded two, 102 and 93 citations, respectively. Of these, a total of 28 citations appeared to be reports of the therapeutic use of hydroxyurea for psoriasis. None appeared to be RCTs. References from reviews identified by this search were, however, scrutinised, and two RCTs not located by any of the above

search procedures were identified. One of these RCTs[165] was excluded because the details of the study have never been fully reported and because the comparison was with daily methotrexate, a regimen that has been abandoned in favour of weekly dose schedules, which have been shown to be less prone to cause hepatic fibrosis (see appendix 3).

Characteristics of included study

One RCT fulfilled the criteria for inclusion.[166] Its design and findings are summarised in *Table 39*.

Results

The included study showed that the probability of psoriasis improvement after 4 weeks of therapy was much greater with hydroxyurea than with placebo. The degree of improvement, however, cannot be judged from this study. The order in which each patient received active treatment is not clear from the published tables.

The study allowed for the continuation of hydroxyurea therapy in an open assessment. The authors commented that it took about 6 weeks for maximal improvement to be achieved.

Discussion

Hydroxyurea has been used to treat psoriasis for nearly 30 years. The conclusions about hydroxyurea are hampered by a lack of good RCT evidence, particularly relating to the degree of improvement. Because hydroxyurea has not been nearly so widely used as other treatment modalities and it has been seen necessary to use this drug in combination with other powerful anti-psoriatic drugs, it would appear that dermatologists have not found hydroxyurea to be as potent as treatments such as methotrexate, cyclosporin or photochemotherapy (PUVA). The available data do not allow a direct comparison of hydroxyurea with these treatments. Hydroxyurea has the advantage that it may often be used in patients for whom these other treatments are contraindicated.

Fumaric acid esters (fumarates)

Summary

Oral fumaric acid ester therapy is an effective systemic treatment for psoriasis.

Of the constituents of the standard compound fumaric acid ester therapy used in Northern Europe (Fumaderm®), dimethylfumarate appears to be the component with the principal anti-psoriatic activity. Monoethylfumarate on its own has not been shown to have any beneficial effect. No differences in efficacy between Fumaderm and dimethylfumarate monotherapy have been demonstrated.

The incidence of symptomatic side-effects (flushing and gastrointestinal disturbance) is high but results in the discontinuation of therapy in less than 10% of patients. Serious side-effects appear to be rare.

Formal comparisons with topical or other systemic therapies have not been performed.

Background

For some 20 years, fumaric acid esters have been used widely in Northern Europe, particularly in German-speaking countries, as a systemic treatment for severe psoriasis. Their use has recently been reviewed.[167] They were introduced by Schweckendiek,[168] a chemist by profession and a psoriasis sufferer, who hypothesised that fumaric acid esters might be beneficial for the disease. He experimented on himself with various forms of fumaric acid and developed a mixture of esters with a higher bioavailability following oral ingestion than fumaric acid itself. He found that these esters improved his own psoriasis, and in 1959 he published his conclusions.[168] As a result of his advocacy, the treatment was taken up by a number of dermatologists in Switzerland, Germany and The Netherlands, and subsequently became popular in those countries. By 1996, one clinic alone had used fumaric acid esters to treat more than 2000 patients.[169] A recent open prospective multicentre study from Germany found that, in 101 patients with extensive chronic plaque psoriasis (PASI ≥ 12), the PASI score could be reduced by an average of 80% after 4 months of therapy with fumaric acid esters.[170]

There have been concerns, however, over safety. Since the late 1980s, fumaric acid ester therapy has been subjected to evaluation in a number of randomised clinical trials.

The commercially available preparation of fumaric acid esters, Fumaderm, consists of a defined mixture of dimethylfumarate and the calcium, magnesium and zinc salts of monoethylfumaric acid. Dimethylfumarate is rapidly hydrolysed *in vivo* to monomethylfumarate, which is thought to be the main active metabolite. These compounds have been shown to have effects both on keratinocytes and on lymphocytes,

TABLE 39 *Design and outcome of trial of hydroxyurea versus placebo*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Leavell, 1970[166]	Hydroxyurea, 1.0 g/day	Placebo	DB, crossover, 8 weeks	10:10	"Severe recalcitrant psoriasis unresponsive to previous treatment"	"Improvement" as judged by the investigator and the patient	7/10:1/10 (per investigator) 9/10:1/10 (per patient)	0.60 (0.26 to 0.94) 0.80 (0.54 to 1.06)

although the latter effects have been thought to be of greater importance. These effects may be summarised as promoting the secretion of Th2-type cytokines (IL-4, IL-5 and IL-10) and inhibiting Th1 cytokines (interferon-γ), a switch in the cytokine profile that appears to be beneficial in psoriasis.

More than two-thirds of treated patients develop gastrointestinal symptoms, including dyspepsia and diarrhoea. One-third of patients develop flushing, a problem that tends to subside with continued therapy. A reduction in circulating lymphocyte numbers is almost universal and exceeds 50% of baseline in about 10% of treated patients.[167] In the past, there have been case reports of acute renal failure, but there has been no evidence of significant impairment of renal function in more recent studies using established treatment protocols. Some groups have reported elevation of liver enzymes, but this effect has not been observed by all.[167]

Search results

A total of 20 citations linking fumaric acid ester therapy with psoriasis were identified by our standard search strategy. Titles and abstracts were read by two people individually to identify possible RCTs. Thirteen citations appeared to be reports of the therapeutic use of fumaric acid ester therapy for psoriasis. One of these examined the topical use of fumaric acid, and five citations were case series or retrospective reviews. One citation was a large open prospective study.[170] Six citations appeared to be reports of controlled studies. One report was excluded because it was a duplicate publication (see appendix 5). The remaining six reports were retrieved and read. One report was excluded because it dealt with psoriatic arthritis (see appendix 5). Four reports containing five RCTs and six comparisons remained for inclusion in the review.

Characteristics of included studies

The characteristics of the trials are summarised in *Table 40*.

Two RCTs compared the compound fumaric acid ester regimen that has become standard in Northern Europe (Fumaderm) with placebo.[171,172] Two RCTs compared two different fumaric acid ester monotherapies with placebo.[173] Two RCTs compared Fumaderm or its equivalent with other fumaric acid ester regimens.[172,174]

Results

The results of the various studies are summarised in *Table 40* and in *Figures 12* and *13*.

Altmeyer and colleagues[171] confirmed the earlier study of Nugteren Huying and colleagues[172] that compound oral fumaric acid ester therapy is an effective treatment for psoriasis. In the former study, mean PASI scores fell with active therapy by 50% (from 21.57 to 10.77) over 16 weeks, but scores remained constant with placebo. Of 49 treated patients, 28 (57%) achieved at least a 70% reduction in PASI score, whereas only 5 of 50 controls (10%) showed similar improvement in the placebo group. In the latter study, 9 of 12 patients showed improvement ($n = 3$) or clearance ($n = 6$) with active therapy, compared with only one patient showing improvement with placebo.

The incidence of symptomatic side-effects was high, although these were often short-lived. Although flushing was universal among the Nugteren Huying study's 12 treated patients,[172] only 21 individual episodes of flushing over the time course of the study were reported by the Altmeyer study's 49 patients.[171] Episodes of diarrhoea, abdominal pain or cramps were reported 21 times. Four of 49 patients (8%) withdrew from the Altmeyer study because of side-effects.[171] A similar incidence of side-effects was found in the larger open study by Mrowietz and co-workers.[170] A trend of lowered lymphocyte counts and raised eosinophil counts was seen in both studies,[170,171] but no serious side-effects were encountered in either study.

Nieboer and colleagues[173] showed that, of the components of the standard compound fumaric acid ester therapy used in Northern Europe (Fumaderm), dimethylfumarate appeared to be the constituent with the principal anti-psoriatic activity. Monoethylfumarate was not shown to have any beneficial effect. In a subsequent study,[174] the investigators were unable to show a difference in efficacy between Fumaderm and dimethylfumarate, supporting their earlier conclusion that dimethylfumarate was the principal active constituent. These conclusions are supported by the study by Nugteren Huying and colleagues,[172] who removed dimethylfumarate from the standard compound preparation and replaced it with monooctylfumarate, and appeared to thereby abolish the therapeutic effect.

Discussion

Fumaric acid ester therapy for psoriasis has achieved widespread popularity in Northern Europe. Although this therapy may have troublesome side-effects when first initiated, it appears that these side-effects tend to settle down in most

TABLE 40 *Design and outcome of trials of fumaric acid ester therapy*

Trial	Intervention	Comparator	Design and duration	*n:n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Altmeyer, 1994[171]	Fumaderm,* escalating dose up to 6 tablets daily	Placebo	DB, parallel group, 16 weeks	49:50 (calculated from figures reported in paper)	Chronic plaque, guttate or erythrodermic psoriasis affecting ≥ 10% BSA; duration of > 2 years; and insufficient response to topical therapy	≥ 70% reduction in PASI (good improvement or complete clearing)	28/49:5/50	0.47 (0.31 to 0.63)
Nugteren Huying, 1990[172]	Fumaderm, escalating dose up to 6 tablets daily	Placebo	DB, parallel group, 16 weeks	12:12	Stable psoriasis affecting ≥ 10% BSA	Complete clearance	6/12:0/12	0.46 (0.17 to 0.75)
Nieboer, 1989[173]	MEFAE-Na, 60 mg, 1–4 capsules daily	Placebo	DB, parallel group, 16 weeks	19:19	Stable nummular or chronic plaque psoriasis affecting ≥ 10% BSA	> 50% improvement based on simplified PASI score	1/19:2/19	–0.05 (–0.22 to 0.12)
	DMFAE, 60 mg, 1–4 capsules daily	Placebo	DB, parallel group, 16 weeks	22:20			6/22:0/20	0.26 (0.06 to 0.45)
Nugteren Huying, 1990[172]	Fumaderm, escalating dose up to 6 tablets daily	OHFAE, 284 mg; MEFAE-Mg, 5 mg; MEFAE-Zn, 3 mg	DB, parallel group, 16 weeks	12:10	Stable psoriasis affecting ≥ 10% BSA	Complete clearance	6/12:0/10	0.45 (0.16 to 0.75)
Nieboer, 1990[174]	Fumaderm, equivalent of 1–4 tablets daily	DMFAE, 120 mg, 1–4 tablets daily	DB, parallel group, 16 weeks	23:22	Chronic plaque, "macular" or guttate psoriasis affecting ≥ 10% BSA	> 50% improvement based on simplified PASI score	12/23:10/22	0.07 (–0.22 to 0.36)

DMFAE, dimethylfumaric acid ester; MEFAE-Na, sodium salt of monoethylfumaric acid ester; MEFAE-Ca, calcium salt of monoethylfumaric acid ester; MEFAE-Mg, magnesium salt of monoethylfumaric acid ester; MEFAE-Zn, zinc salt of monoethylfumaric acid ester; OHFAE, octyl hydrogen fumaric acid ester

* *Fumaderm consists of DMFAE, 120 mg; MEFAE-Ca, 87 mg; MEFAE-Mg, 5 mg; and MEFAE-Zn, 3 mg*

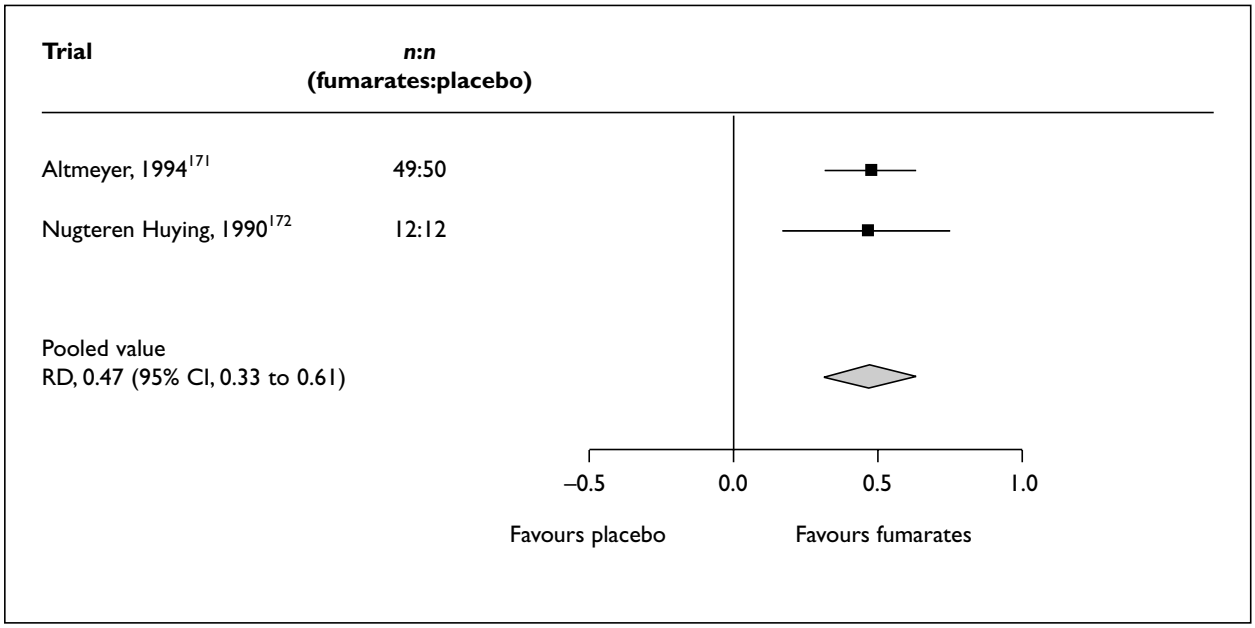

FIGURE 12 *Mixed fumaric acid esters versus placebo: RDs (95% CI)*

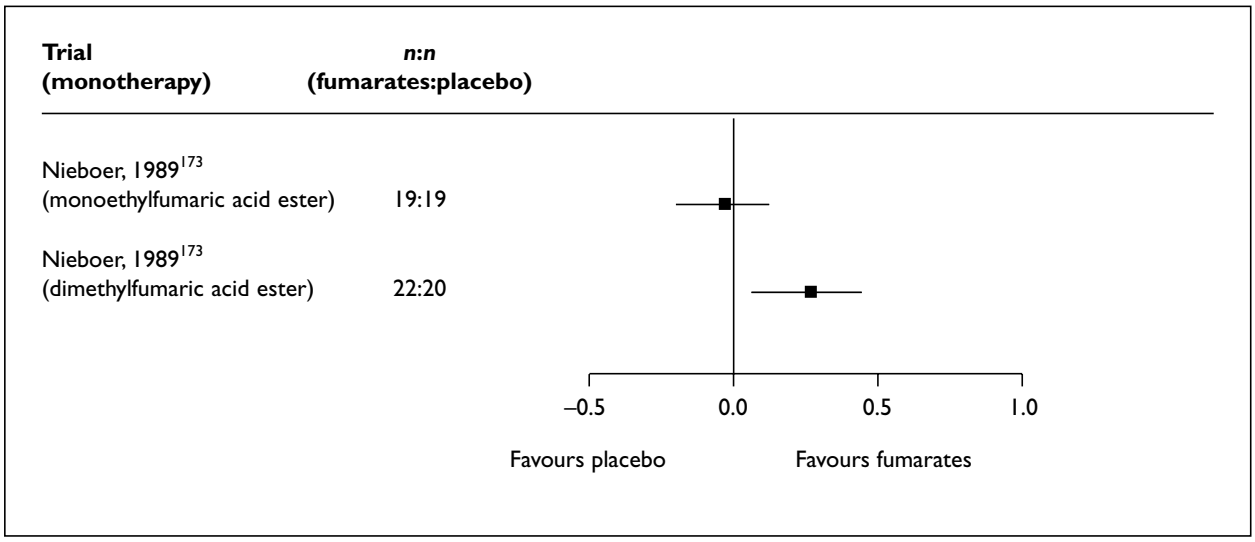

FIGURE 13 *Fumaric acid ester monotherapy versus placebo: RDs (95% CI)*

patients. The incidence of serious adverse events appears to be low.

The active moiety of the commonly used regimen appears to be dimethylfumarate. Further studies are required to determine whether there is benefit in terms of increased efficacy or reduction in the incidence of side-effects from the concomitant use of monoethylfumarates. It is probable that efficacy would be increased further by the combination of fumaric acid ester therapy with topical medication, for instance, vitamin D_3 analogues. Comparative studies with other systemic therapies have not been performed.

Azathioprine

Summary

Oral azathioprine is a sporadically used and moderately effective systemic therapy for severe psoriasis. Side-effects are mainly myelosuppression, nausea and vomiting. No RCTs of azathioprine for the treatment of psoriasis have been performed, nor comparative studies with other therapies.

Background

Azathioprine is a synthetic purine analogue synthesised by attaching 6-mercaptopurine to an imidazole ring. It has been available

for nearly 40 years, and its principal clinical application is in the prevention of solid organ graft rejection. However, with the advent of cyclosporin, the use of azathioprine for this indication is diminishing. Azathioprine is used extensively in dermatology, particularly as a steroid-sparing immunosuppressive agent to treat diseases such as bullous pemphigoid, pemphigus vulgaris, lupus erythematosus and severe atopic eczema.[175]

In vivo, azathioprine is converted predominantly to its active metabolite 6-mercaptopurine by hepatic xanthine oxidase. Most individuals are fast metabolisers of azathioprine, but slow metabolisers are at risk of azathioprine toxicity, a polymorphism for which testing can be performed. 6-Mercaptopurine blocks purine biosynthesis, and this blockade inhibits rapidly dividing cells. As a consequence, azathioprine has immunosuppressive properties, more specifically, the ability to inhibit T cell-mediated immunity.

The most important adverse effect of azathioprine is dose-related bone marrow suppression, of which leucopenia is the most common. Nausea and vomiting may be dose limiting.[175] Levels of liver enzymes rise rarely but should be monitored; however, when azathioprine is used as a low-dose monotherapy for the treatment of psoriasis, the risk of malignancy is very low. Rarely, the use of azathioprine in treating psoriasis has been associated with atrial fibrillation.[176]

The first and largest study of the use of azathioprine in the treatment of psoriasis was performed by du Vivier and co-workers in 1974.[177] In this uncontrolled study, 19 of 29 patients with severe psoriasis were reported to have benefited from azathioprine administered at a dose of 100–300 mg/day, with the recommended daily dose being 150 mg. Other reports[178–182] are no more than case studies, particularly involving psoriasis that has occurred concomitantly with bullous pemphigoid.[183,184] Overall, it would appear that azathioprine is less effective than either methotrexate or cyclosporin as a treatment for severe psoriasis.

Search results

A broad search was undertaken to identify all records containing the terms 'azathioprine' and 'psoria*' that were cited in the Cochrane Controlled Trials Register 1999, MEDLINE from 1966 to 1999 and EMBASE from 1980 to 1999. A total of 14 citations appeared to be reports of the therapeutic use of azathioprine for psoriasis. None appeared to be RCTs. Thus, no trials could be included.

Discussion

Reports of the use of azathioprine in the treatment of psoriasis are sporadic, and most are from the 1970s. Only one large, but uncontrolled study was found. We must conclude that there is currently no good evidence that azathioprine is an effective treatment for psoriasis. Furthermore, the fact that azathioprine is rarely used today for treating severe psoriasis would lead us to speculate that it is not as effective as methotrexate, cyclosporin or PUVA. However, there have been no studies directly comparing the use of azathioprine with other systemic therapies used for treating severe psoriasis.

Sulphasalazine

Summary

Sulphasalazine is an inexpensive anti-inflammatory agent composed of sulphasalazine and 5-aminosalicylic acid. The daily oral dose is 3–4 g, and about 25% of patients suffer side-effects, notably nausea, vomiting and rashes. Based on the results of one RCT, sulphasalazine appears to be a moderately effective treatment for severe psoriasis, although probably less so than acitretin, cyclosporin, PUVA and methotrexate. Further RCTs are justified to compare sulphasalazine with placebo and with other systemic therapies.

Background

Sulphasalazine is an anti-inflammatory agent, 5-{[*p*-(2-pyridylsulfamoyl)phenyl]azo} salicylic acid. It is commonly used in the treatment of inflammatory bowel disease,[185] and is an effective and widely prescribed second-line treatment for rheumatoid arthritis.[186] One of the anti-inflammatory properties possessed by sulphasalazine is that of inhibiting 5-lipoxygenase. Because psoriasis plaques are characterised by elevated 5- and 12-lipoxygenase activity, it is thus logical to consider sulphasalazine as a treatment. It is debatable which component of sulphasalazine is the active moiety. After oral administration, sulphasalazine is partially absorbed and extensively metabolised. Approximately one-third of a dose of sulphasalazine is absorbed from the small intestine, and the other two-thirds pass to the large intestine. In the colon, sulphasalazine is split into its two main components: 5-aminosalicylic acid and sulphasalazine. Most of the sulphasalazine is absorbed, compared with only about one-third of 5-aminosalicylic acid. Thus, the systemic

anti-inflammatory effects of sulphasalazine are most likely related to the parent compound and/or sulphasalazine.

Sulphasalazine therapy is associated with a number of side-effects, which are more common at higher doses of the drug. The most common side-effects are headache, nausea and vomiting, which occur in about one-third of patients. Reversible oligospermia may occur in at least one-third of men treated with sulphasalazine. Less frequent side-effects include rashes, pruritus and haemolytic anaemia (associated particularly with glucose 6-phosphate dehydrogenase deficiency).

Sulphasalazine is prescribed at an initial dose of 500 mg daily for 3 days; if tolerated, the dose is usually increased to 1 g taken three times daily. The maximum dose is 1 g taken four times daily. Regular blood monitoring is required to screen for haemolysis and occasional hepatitis.

An open study performed by Gupta and co-workers[187] examined the efficacy of sulphasalazine (3 g daily for 8 weeks) in patients with chronic plaque psoriasis. Out of the original 32 patients, 24 patients completed the study, and 19 of these patients had modest-to-marked improvement or clearing of their psoriasis.

Search results

A total of 11 citations linking sulphasalazine with psoriasis were found by our standard search technique. Titles and abstracts were read by two people (CMC and CEMG) to identify possible RCTs. Two citations appeared to be reports of the therapeutic use of sulphasalazine in psoriasis, as opposed to psoriatic arthritis, and one of these was an RCT.

Characteristics of included study

One RCT fulfilled the criteria for inclusion, and its design and findings are summarised in *Table 41*.

Results

The included study[188] showed that 8 weeks of treatment with sulphasalazine (3–4 g daily) produced a moderate improvement in 41% and a marked improvement in 41% of 17 assessable patients, compared with only one patient with moderate improvement (4%) of the 27 patients receiving placebo. Moderate improvement was defined as a global improvement in psoriasis of 30–59%, and marked improvement as a global improvement of 60–89%. Six patients (of the original 23 patients) withdrew from the study because of side-effects: four patients with cutaneous eruption and two patients with nausea. This study allowed responders to treatment (14 patients) to continue on sulphasalazine in an open manner for a further 4 weeks, with continued improvement.

Discussion

On the basis of the one RCT, it appears that sulphasalazine, at doses of 3–4 g daily, is an effective treatment for moderate or severe chronic plaque psoriasis. This observation should be tempered by the observation that about 25% of patients find the side-effects significant and are unable to continue taking the drug. Marked improvement (i.e. ≥ 60%) occurs in about 40% of the patients who can tolerate the drug. The side-effects are generally not severe in nature and thus make sulphasalazine a useful alternative systemic therapy in patients who are either unwilling to use or do not justify the risk of therapies such as PUVA, methotrexate or cyclosporin.

TABLE 41 *Design and outcome of trial of sulphasalazine*

Trial	Intervention	Comparator	Design and duration	*n*:*n* (intervention: comparator)	Inclusion criterion (disease severity)	Success criterion	Response rate (intervention: comparator)	RD (95% CI)
Gupta, 1990[188]	Sulphasalazine, 3–4 g daily	Placebo	DB, parallel group, 8 weeks	23:27	Moderate/severe stable psoriasis	≥ 60% improvement, based on global score	7/23:0/27	0.30 (0.11 to 0.49)

Chapter 8

Costs and cost-effectiveness

Summary

Several analyses of psoriasis treatment have been published, but none has so far provided a sound basis for decision-making or for the formulation of prescribing guidelines in the UK. Nevertheless, these studies have identified some of the problems associated with economic analyses of psoriasis treatment.

Studies to establish the cost-effectiveness and cost–utility of all the treatments for severe psoriasis in the UK are needed.

Background

Psoriasis affects approximately 2% of the UK population. If all these patients were to be treated, the costs would likely involve a substantial use of NHS resources. The assessment of cost-effectiveness in psoriasis treatment is difficult, bearing in mind the number of factors that need to be accounted for. Such factors are drug acquisition costs, the tendency for dermatologists to use combination therapies, poor adherence to therapy (especially topical), the chronic nature of the disease (interspersed with remissions) and the need to consider concerns about qualify of life. The long-term nature of psoriasis and potential for prolonged use of systemic therapies bring with them the attendant costs contingent on monitoring for side-effects, which may only manifest after many months of treatment (e.g. skin cancers in patients treated with PUVA and liver toxicity in those receiving methotrexate). The difficulty in interpreting costs in the context of different national healthcare systems is immense. In the USA, for instance, there are direct financial costs to the patient, which are not appreciated by patients treated under the NHS. Indirect costs are notoriously difficult to estimate. For instance, one treatment may enable a patient to return to work or full-time education sooner than another. So-called 'intangible costs' associated with lowered quality of life need to be accounted for in cost–utility analyses. Finally, the cost-effectiveness of a particular therapy can be interpreted quite differently depending on the perspective of cost to the NHS or to the patient. There is little doubt that the subject of the pharmacoeconomics of treatments for severe psoriasis deserves a structured, thoughtful approach that is cognisant of the potential pitfalls.

Search results

Nine reports of economic analyses of psoriasis treatment were found. These studies are listed in *Table 42*. The studies themselves do not necessarily refer to the treatment of severe psoriasis and do not fulfil RCT criteria. However, it was considered important to present them here, if only to underscore the relative paucity of cost–benefit and cost–utility data in the management of psoriasis, let alone severe psoriasis.

An economic analysis considers both the inputs and the consequences. The majority of the studies in this review considered only the input costs and are therefore better described as cost analyses.

Cork[189] reported a preliminary, retrospective study of the economic impact of the introduction of calcipotriol in the UK. Referral patterns did not change, but the number of inpatient admissions was reduced by 50% (for one consultant). That hospital also experienced a 75% reduction in the use of UVB phototherapy, a 60% reduction in the use of methotrexate and a 50% reduction in the use of psoralens for UVA. According to the author, these observations suggested that calcipotriol use obviated the need for second-line therapies such UVB and methotrexate. However, it seems likely that this was a 'new drug phenomenon' caused by a change in prescribing patterns, which would have been shown had there been a rigorous evaluation of the patient outcomes as well as the input costs.

Krueger and colleagues[190] reported estimated costs for outpatient and inpatient treatment of psoriasis, but gave no details of the methods used to gather the data. Patients with psoriasis were reported to spend US$650 per year on medication costs, laboratory tests and physician fees. Inpatient treatment was estimated to cost US$10,500 per year (on the basis that each hospital stay lasted 21 days, at a cost of US$500 per day).

TABLE 42 *Economic analyses of psoriasis treatment*

Trial and country	Study type	Treatments included	Methods
Chen, 1998[197] USA	Cost-effectiveness (cost–utility) and cost–benefit analyses	Methotrexate vs Goeckerman therapy	Utility values determined by VAS and willingness to pay
Cork, 1993[189] UK	Cost analysis	Impact of the introduction of calcipotriol on UVB/tar and PUVA treatment costs	
Davies, 1997[198] UK	Cost-effectiveness analysis	CSA, dithranol and UVB	
Einarson, 1994[196] Canada	Cost-minimisation (cost-effectiveness) analysis	CSA, methotrexate, retinoids and PUVA	Meta-analysis to derive summary estimates of clinical success, relapse rates and side-effects, plus decision analytical modelling
Ellis, 1987[194] USA	Cost-effectiveness analysis	Etretinate vs inpatient treatment	
Feldman, 1997[191] USA	Cost analysis	All (not specified)	
Krueger, 1984[190]	Cost estimates	All (not specified)	
Sander, 1993[192] USA	Cost analysis	Phototherapy (Goeckerman, PUVA and outpatient UVB) and oral therapy, including methotrexate, etretinate, hydroxyurea and CSA	
Snellman, 1998[195] Finland	Cost analysis	Heliotherapy vs "conventional psoriasis treatment"	

Feldman and colleagues[191] conducted a postal survey of 578 patients with psoriasis to obtain an estimate of treatment costs faced by the patients. Patients were asked to complete a questionnaire covering the time spent on psoriasis care, total charges/expenses, out-of-pocket expense for psoriasis care, number of prescriptions and over-the-counter medicines. Psoriasis severity was assessed using the Self-Administered PASI, which had been previously validated. No results were presented to show the types of therapy that the patients were receiving. The Self-Administered PASI scores correlated positively with total costs ($r = 0.26$, $p = 0.0001$), "bothersomeness" ($r = 0.30$, $p = 0.0001$) and time required for treatment ($r = 0.38$, $p = 0.0001$). It can safely be concluded that costs increased with disease severity.

In the Feldman study, the estimated total annual expense in caring for psoriasis was US$800 per patient,[191] which was similar to Krueger's 1984 estimate of US$650.[190] However, Feldman and colleagues pointed out that their method (which is not described in detail) understates the effect of extreme expense values. As a result, PUVA, Goeckerman therapy and cyclosporin costs may exceed the values that they used; however, no data on comparative treatment costs were presented.

In 1993, Sander and colleagues[192] set out to calculate comparative costs for seven different treatment modalities: Goeckerman therapy, PUVA, UVB, methotrexate, etretinate, hydroxyurea and cyclosporin. For each modality, ten patients who had received it as monotherapy were selected and their records were used to identify costs (except for cyclosporin, for which the records of only six patients were used). The clinical response rate was derived from physicians' global assessments in the medical records and presented as percentage clearance from baseline. The results of the analysis were expressed as annual costs in US dollars (mean and range). Mean costs ranged from US$1131 (for hydroxyurea) to US$6648 (for cyclosporin). The authors concluded that their data would help practitioners and healthcare organisations to select appropriate therapy.

The use of real-life data extracted from medical records should provide a sound basis for economic analysis. However, in the Sander study,[192] records

from only a small number of patients were used, and it is questionable whether the data would be representative for the authors' institution and unlikely that they could be generalised to a wider population. It has been suggested that 25–30 patients in each comparator group could give representative data.[193] Moreover, the authors suggested that the way in which they selected the patients for inclusion biased the results towards successful therapy. Although the authors presented a table of clinical response rates, these rates were not used in the interpretation of the cost data. The final cost comparison compared all regimens as though they were equally effective.

In 1987, Ellis and colleagues[194] investigated the impact of etretinate therapy on inpatient treatment costs in a group of 26 patients with a history of hospitalisation for psoriasis. During the etretinate treatment period, patients were hospitalised for a mean (± SEM) of 0.2 ± 0.1 days per year, compared with 13.8 ± 2.4 days per year during the pre-etretinate treatment period. The authors estimated the corresponding treatment costs to be US$2300 per year and US$10,000 per year, respectively. The calculations for the costs of inpatient treatment (pre-etretinate) did not take account of additional outpatient expenses, lost working days or intangible costs.

In 1998, a Finnish study examined the effect of heliotherapy on the costs of psoriasis.[195] The costs of psoriasis treatment in 46 patients were monitored for 1 year before, during and for 1 year after a 4-week heliotherapy course. The authors concluded that heliotherapy reduced costs only in patients with severe psoriasis who required expensive medication or inpatient treatment. It would be difficult to generalise the results to other populations because the heliotherapy was delivered in the Canary Islands, Spain, while all other costs were related to the Finnish healthcare system.

In 1994, Einarson and colleagues[196] reported an economic analysis of four systemic treatments for severe psoriasis: cyclosporin, methotrexate, etretinate and PUVA. The analysis was conducted from the perspective of the Canadian government as payer. A decision–analytic model was constructed and used as the basis for the calculations. Clinical outcome data for the model were derived from meta-analysis of the literature. Overall costs included the costs of drug acquisition, drug administration, routine medical care, adverse event management and laboratory tests.

The authors concluded that cyclosporin was the most cost-effective treatment for severe psoriasis. The dose of cyclosporin was 5 mg/kg/day for a period of 6 weeks. The authors also pointed out that, because of the reimbursement paid by the province, their results may not be generalisable to other provinces or countries. Two other criticisms may be levelled at this study. First, some details of the methods to calculate cost avoidance were not explicit. Second, the trials used for the meta-analysis of etretinate therapy concerned mainly palmoplantar pustular psoriasis, and the methotrexate data were based on a single study. This study is probably best described as a cost-minimisation analysis.

In 1998, Chen and colleagues[197] reported a cost-effectiveness and cost–benefit analysis of using methotrexate versus Goeckerman therapy for psoriasis. They constructed a decision–analytic model and included a measure of patient preference (utility) in their calculations. The authors concluded that, in severe psoriasis, only methotrexate demonstrated a net benefit. The results of the cost-effectiveness analysis, which may be better described as a cost–utility analysis, were highly sensitive to the utilities used. Utilities were generated from three groups: patients, healthy non-experts and dermatologists. The cost-effectiveness analysis showed that, for all three groups, Goeckerman therapy should be chosen in preference to liquid methotrexate for severe psoriasis. This finding contrasted with the cost–benefit analysis, which suggested that liquid methotrexate rather than Goeckerman therapy should be provided for psoriasis of all grades of severity.

Davies and colleagues[198] in the UK compared the benefits, risks and costs of cyclosporin treatment with day-care treatment. They reported that the average total cost to treat a patient for 1 year with short-course cyclosporin at 5 mg/kg/day was £1473, whereas the corresponding day-care treatment cost was £2815.

Discussion

Most of the studies in this review are cost analyses, rather than economic analyses, in the accepted sense of the term. Moreover, the fact that they have been conducted in different countries, concerning different interventions from 1984 to 1998, means that the results are not comparable.

The study by Sander and colleagues[192] may provide a basis for future studies. The strength of their study lies in the fact that cost data were derived from 'real-life' samples of psoriasis patients. Unfortunately, its weakness was that the samples (ten patients for each treatment except cyclosporin, for which there were six patients) were too small to be reliably representative. However, a similar protocol, with refinements to correct the shortcomings of the original study, could yield useful results about real-life costs, which could then be used for theoretical economic modelling.

Three studies involved the construction of decision–analytic models as the basis for calculations.[196–198] These studies are not directly comparable because they addressed different interventions in different countries and drew the data for the model from different sources. Nevertheless, they serve to identify some of the problems associated with economic analyses of psoriasis treatment and suggest avenues for future research.

Chen and colleagues[197] included utilities in their analysis, which they generated from patients, healthy non-experts and dermatologists. They noted that patients' preferences for interventions differed markedly from those of dermatologists, although they did not differ significantly from those of "society" (healthy non-experts). As a result, therapies were least cost-effective when using dermatologists' preferences. This observation has important implications for future economic analyses, if we assume that a similar pattern would apply in other countries. The range of interventions available for the treatment of severe psoriasis includes expensive products and relatively inexpensive products that may be expensive to use because of the time, labour or equipment required. Furthermore, for some products, the additional costs of monitoring and/or treating side-effects must be considered. Cost-effectiveness studies will be of interest to purchasers and will provide a helpful basis for the comparison of treatments; however, given the growing understanding of the wider psychosocial effects of psoriasis, the most useful economic analysis will be a cost–utility analysis. Ideally, this analysis should use patients' (or society's) preferences and include all the treatments that are routinely offered to patients with severe psoriasis.

Chapter 9

Summary

Psoriasis is a common disease that affects 2% of the population of the UK. Although severe psoriasis – the treatment of which is the object of this systematic review – accounts for only about a quarter of cases, (i.e. those that are treated in the secondary care sector), the prevalence of moderate-to-severe psoriasis is still equivalent to that of either rheumatoid arthritis or diabetes mellitus. Both rheumatoid arthritis and diabetes mellitus are perceived as common, disabling and perforce important autoimmune diseases, and they probably attract more notice and resource than does the management of psoriasis. The high prevalence of psoriasis, coupled with its chronic, recalcitrant nature and consequent severe psychosocial disablement, mean this disease is a major detriment to the nation's health. Although a majority of patients can be treated in the primary care sector, the main NHS resources for psoriasis treatment probably reside within secondary care (e.g. inpatient treatment, phototherapy and systemic drugs with their attendant requisite safety monitoring). Thus, a working knowledge of which treatments for severe psoriasis are effective and safe, based on firm evidence, is imperative for decision-makers in the NHS. Furthermore, the results of this review should be used by support groups for patients with psoriasis to identify deficits in the uptake or use of therapies that have little or no evidence base for their effectiveness. We have consulted with the two such support groups in the UK: the Psoriasis Association and the Psoriatic Arthropathy Alliance.

Firm RCT-based evidence of efficacy could be reliably demonstrated for only five therapies for severe psoriasis.

Cyclosporin

There is strong RCT evidence to support the use of cyclosporin, which is usually effective for inducing the remission of psoriasis in the dose range of 2.5–5.0 mg/kg/day. Doses above 5.0 mg/kg/day are associated with increased side-effects, which mitigate any dose-related gains in efficacy. Maintenance treatment requires a dose of 3.0–3.5 mg/kg/day and is most effective if given continuously as opposed to intermittently.

Retinoids

Retinoids are a moderately effective monotherapy at doses of 75 mg/day or 1 mg/kg/day. Acitretin is as effective as etretinate, which is less effective than cyclosporin. There is good RCT evidence to support the use of combination treatment with a retinoid and PUVA, which is more effective than retinoid alone and offers the advantage of lowering the cumulative UVA dose.

Phototherapy and photochemotherapy

PUVA using oral psoralen (8-MOP, 0.6–1.0 mg/kg) is effective in clearing psoriasis. PUVA using topical psoralen (bath PUVA) is equally effective; however, UVA alone does not clear psoriasis.

UVB phototherapy is effective in clearing psoriasis. NBUVB (311 nm) offers the possibility of clearance with fewer episodes of erythema and may require a lower cumulative dose of UVB. It is not yet known how NBUVB compares with PUVA. The combination of PUVA or UVB with retinoids appears to be more effective than either treatment alone.

There are no evaluable RCTs that compare the effects of adding topical tar to either PUVA or UVB with PUVA, or to UVB alone.

PUVA is as effective as daily dithranol in clearing psoriasis, but there are no trials that evaluate the effects of adding PUVA to dithranol treatment.

Combination treatment using phototherapy or photochemotherapy with a vitamin D_3 analogue is more effective than either treatment alone.

Fumarates

Oral fumaric acid ester (fumarate) therapy is an effective systemic treatment for psoriasis.

Dimethylfumarate appears to be the principal active component.

Definitions, outcomes and side-effects

We soon found that a definition of 'severe psoriasis' is not universal, although the one used for this report is, we believe, acceptable and based on clinical criteria. Ideally, a definition of 'severe psoriasis' must also encompass previous historical response to treatment and psychosocial disability – an area that we are actively researching.[199] We were forced to choose clinical severity as the measure of severity because other determinants (i.e. response to treatment and psychosocial disability) are not currently in wide use. Severe psoriasis can usually be defined as psoriasis involving at least 20% of the body surface area and/or a PASI score of 12 or more, although treatments covered in this review can be used if the body surface area involved or PASI values are smaller. There is little doubt that more rigorous standardisation of outcome measures and an accepted definition of severe psoriasis are required for this area of research. Such outcome measures and definitions should be an integral part of any future planning of therapeutic interventions in the management of psoriasis. The outcome measures employed in the studies included in this review were extremely varied (e.g. PASI, body surface area and global scores) and were presented in ways that could not easily be conveyed as response to treatment, or as percentage or absolute reduction in severity score.

It is apparent that the bulk of outcome measures (however unsatisfactory they may be) used in clinical studies are very much clinician determined. Whether these outcomes have relevance to the patient is for the most part unknown. This oversight is common to many clinical studies, and it would be pertinent to perhaps include the aforementioned patient support groups in the planning of future studies. In defence of the pharmaceutical companies, who so often drive such trials, it is apparent that they are now assigning more importance to subjective outcome measures such as quality of life. This is particularly important when one realises that the clinical severity of psoriasis (i.e. PASI or surface area of the skin involved) does not necessarily correlate with psychosocial disability. The other outcome measure currently under-utilised, but one that is desperately important to those responsible for service provision, is that of cost-effectiveness. There are no RCTs of cost-effectiveness/cost–utility in the management of psoriasis. Pharmacoeconomic measures have only recently been introduced into clinical trials of drug therapy for psoriasis. There is an increasing demand for economic analyses of treatment as a means of discriminating between products that are safe and efficacious. This demand is in part driven by the National Institute for Clinical Excellence (NICE) and Hospital Medicines Management Groups. Studies of cost-effectiveness and cost–utility will be particularly useful to provide information for decision-making.

Many studies appear to be underpowered and missing relevant treatment arms, which are highly pertinent to a clinician but may be conveniently omitted by pharmaceutical companies sponsoring the research. Few long-term studies are available, and there is a need for more of these, particularly with an eye to side-effects, which may not manifest in short-term studies.

The reporting of side-effects was low overall in the trials assessed for this review. This fact was surprising, bearing in mind the potential toxicity of most of the drugs, and is possibly a reflection of inclusion and exclusion criteria homogenising the study population and lowering the risk, at least of short-term side-effects. It is possible that pharmacogenetics – the study of how genetic differences influence the variability in patients' responses to drugs – may obviate some safety issues, as in future, only patients with the requisite 'genotypic profiles' would receive certain drugs. There was little mention of clinical safety/tolerance of drugs in relation to effectiveness in the trial reports. As an example of outstanding questions, are patients (especially women) with psoriasis who are treated with cyclosporin happy to have hypertrichosis in return for clinical improvement of psoriasis? In the case of hydroxyurea, although the RCT evidence is not available to state that this drug is effective in treating psoriasis, 45–80% of patients think that it is. In the long term, what do patients consider to be an acceptable risk? Using cyclosporin as the exemplar, is the risk of renal impairment acceptable for continued control of their psoriasis? The patients' viewpoint is critical and should not be underestimated. They may be willing to take what to clinicians are unacceptable risks in exchange for a vastly improved quality of life.

Thus, although this systematic review has attempted to be an exhaustive examination of current evidence and RCTs, we often found that

the important outcomes, irrespective of RCT status, had not been measured. Drugs that are generic (e.g. methotrexate and hydroxyurea) suffer in the world of the RCT because the necessary industrial funding is not forthcoming. Pharmaceutical companies are undoubtedly mainly interested in new developments and the marketing of novel therapies that have the edge over those of their competitors. It is apparent from this review that systemic therapy is becoming more popular for psoriasis treatment, a movement that is driven by patients themselves and by the advances being made in our understanding of the molecular genetics and basic pathomechanisms that determine this enigmatic disease. Hopefully, progress in the area will be to the extent that newer, better and safer therapies will supersede those referred to in this review. For instance, T cell-targeted approaches, which selectively inhibit T cell activation via blockade of co-stimulatory or accessory molecules, are already in advanced clinical trials,[200] as is cytokine modulation. The administration of Th2 cytokines, such as IL-10,[201] may normalise (i.e. switch) the predominant Th1 cytokine imbalance present within psoriatic plaques. Attempts are being made to minimise the long-term toxicity of systemic retinoids by the use of retinoid mimetic drugs (e.g. liarozole)[202] that block the metabolism of retinoic acid, leading to increased endogenous levels of retinoic acid. It is probable that new therapies will be used to either clear disease rapidly (i.e. as good short-term treatment) or maintain improvement (i.e. as long-term treatment).

Chapter 10

Conclusions

Ascertaining whether or not a treatment is effective in the management of severe psoriasis is undoubtedly worthwhile. With declining resources available for the management of chronic inflammatory skin diseases such as psoriasis and atopic dermatitis, it is imperative that the choice of treatment is guided by a firm evidence base. Such an evidence base can only accrue from a systematic review of RCTs of such treatments. To our knowledge, there is only one published systematic review[203] of treatments for severe psoriasis; however, this particular report is unsatisfactory, mainly because of the inclusion of non-randomised studies. The current report has concentrated on determining, through systematic review, which systemic therapies are effective in the management of severe psoriasis. It is the view of the authors of this report that such a systematic review is limited by nature of the time constraints imposed. The need for such constraints (i.e. a timely report and one pertinent to current clinical practice) is, however, fully understood by the authors.

Early studies of drugs, some of which are now generic, such as methotrexate, are understandably lacking in the rigour represented by RCTs. However, methotrexate is a well-accepted treatment for severe psoriasis, and lack of such RCTs must not be used to penalise such treatment unjustly. We acknowledge that reliance on pooled RDs is suboptimal, and a more extensive investigation of heterogeneity may have provided more information.

In total, 111 RCTs were found regarding the use of cyclosporin, systemic retinoids, phototherapy and photochemotherapy (including UVB and PUVA), methotrexate, hydroxyurea, fumarates, sulphasalazine and combinations of therapies, particularly those involving phototherapy. There are few comparisons between systemic therapies and relatively few combination studies, which is not a true reflection of clinical practice. Most studies were short-term, with poor reporting of side-effects, and long-term studies were rarely designed as RCTs. We were able to define a number of effective interventions and a number for which evidence is lacking. Overall, the costs of treatment of severe psoriasis are very difficult to ascertain, mainly due to the paucity of such studies in the UK as well as the fact that the costings that are available are predominantly from North America, where insurance company and healthcare provider reporting provides for a more accurate database. Furthermore, the situation is complicated by the fact that many drug treatments for severe psoriasis are not unique to the management of this disease. Cyclosporin is used in the prevention of transplant graft rejection and in the management of autoimmune disease, methotrexate is a common drug used in chemotherapy, and systemic retinoids are used to treat ichthyosis and as cancer chemopreventive agents. It is still very possible though to ascertain cost per patient by taking into account individual drug cost and the cost of monitoring. Important comparative data are needed based on the costs of inpatient and day-treatment centres.

The therapeutic modalities assessed by this review can be classified as either having firm evidence for their use or lacking such evidence. It is imperative to note that this does not necessarily preclude the use of accepted management strategies for psoriasis, such as inpatient or day-treatment centre regimens, including Goeckerman and Ingram therapies.

Interventions with firm RCT evidence of efficacy

The interventions for which firm RCT evidence of efficacy can be demonstrated are:

- cyclosporin
- systemic retinoids (acitretin and etretinate), especially in combination with PUVA
- photochemotherapy and phototherapy: PUVA, BBUVB and NBUVB
- combinations of topical calcipotriol and corticosteroids with phototherapy
- fumarates.

Interventions lacking firm RCT evidence of efficacy

The interventions for which firm RCT evidence of efficacy is lacking are:

- methotrexate
- hydroxyurea
- azathioprine
- sulphasalazine.

As previously mentioned, the information on costs of treatment for severe psoriasis is limited, but it is important to ascertain cost-effectiveness on a per-patient basis.

Research recommendations

Standardised assessment of psoriasis severity and outcome measures

There is a perceived need to standardise the assessment of psoriasis severity and outcome measures internationally so that, in future, studies are comparable. Suggested ways by which this could be achieved are listed below.

1. An in-depth study of relevant outcome measures in the treatment of psoriasis could lead to an easily calculated, overall global assessment of the clinical severity of psoriasis (to replace the PASI) and awareness of which outcomes are important to the patient.
2. Further characterisation and analysis of outcome measures that are important to the patient are needed. Such measures may incorporate accepted tools to measure quality of life and psychosocial distress (e.g. dermatology life-quality index and the Short Form with 36 Items [SF-36]).
3. A definition of 'severe psoriasis' should be established. Perhaps this definition should be a holistic one, not only incorporating the clinical severity of psoriasis, but taking into consideration psychosocial disability and historical disease behaviour.

Defined RCTs

A number of defined RCTs are perhaps indicated by this review. In order of priority, these recommended RCTs are:

1. comparison of cyclosporin versus methotrexate
2. comparisons of systemic therapy/phototherapy with inpatient and/or day-treatment centre management
3. comparison of acitretin versus methotrexate as a long-term study
4. both short- and long-term comparisons of fumarates versus methotrexate
5. comparison of NBUVB versus PUVA, relating to both short-term efficacy and long-term safety
6. comparison of hydroxyurea versus placebo
7. comparison of azathioprine versus placebo
8. further comparison of sulphasalazine versus placebo.

In an attempt to mirror the 'real-life' practice of combining topical and systemic therapies, we suggest that trials that focus on this approach would be relevant to the NHS. Furthermore, these and the aforementioned studies should be of sufficient length to ascertain the efficacy of maintenance therapy and risk of long-term side-effects.

It is important to address adequately the importance of cost-effectiveness in the management of severe psoriasis. For instance, although systemic therapies are frequently effective, the drugs themselves and the monitoring of patient safety are costly. Such systemic therapies should be compared on cost in the light of the main comparators, which are either inpatient or day-treatment centre management of psoriasis (including combinations of phototherapy and topical therapies). Any economic evaluation should ideally be of a cost–utility or cost–benefit design.

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Appendix 1

Cyclosporin studies excluded

Study	Reason for exclusion
Bagot M, Grossman R, Pamphile R, Binderup L, Charue D, Revuz J, *et al.* Additive effects of calcipotriol and cyclosporine A: from *in vitro* experiments to *in vivo* applications in the treatment of severe psoriasis. *C R Acad Sci III* 1994;**317**:282–6.	Same data as Grossman *et al.*, 1994[34]
Bayerl C. Treatment of psoriasis vulgaris with etretinate versus cyclosporin A. Report on a study. *Aktuel Dermatol* 1992;**18**:27–31.	Data are a subset of Mahrle *et al.*, 1995[46]
Baykal K, Tastan HB, Gur AR, Kurumlu Z. Intralesional cyclosporin A treatment in localized plaque-type psoriasis. *Deri Hast Frengi Ars* 1994;**28**:199–204.	Intralesional cyclosporin
Blaszczyk M, Glinski W, Jablonska S, Glinska Ferenz M, Rubisz Brzezinska J, Lis A, *et al.* Sequential treatment of severe psoriasis with Cyclosporin A (Sandimmun–Neoral) and topically applied 0,005% calcipotriol. *Przegl-Dermatol* 1997;**84**:135–43.	Not a randomised study of cyclosporin A (cyclosporin A was used in non-randomised prestudy phase)
Bunse T, Schulze HJ, Mahrle G. Topical administration of cyclosporin in psoriasis vulgaris. *Z Hautkr* 1990;**65**:538,541–2.	Topical cyclosporin
Clinical Study Group for Cyclosporin (CSGC). Clinical efficacy of ciclosporin in the treatment of psoriasis: a multicentre double-blind study. *Rinsho Iyaku* 1991;**7**:617–33.	Japanese study (translation still awaited)
Dubertret L, Perussel M, Robiola O, Feutren G. Cyclosporin in psoriasis. A long-term randomized study on 37 patients. *Acta Derm Venereol Suppl (Stockh)* 1989;**146**:136.	Insufficient data for analysis
Engst R, Huber J. [Results of cyclosporin treatment of severe, chronic psoriasis vulgaris.] *Hautarzt* 1989;**40**:486–9.	Insufficient data for analysis
Gajardo J, Villaseca J. Psoriasis and cyclosporine: an attempt at topical treatment. *Rev Med Chil* 1994;**122**:1404–7.	Topical cyclosporin
Gottlieb SL, Heftler NS, Gilleaudeau P, Johnson R, Vallat VP, Wolfe J, *et al.* Short-contact anthralin treatment augments therapeutic efficacy of cyclosporine in psoriasis: a clinical and pathologic study. *J Am Acad Dermatol* 1995;**33**:637–45.	Non-randomised study
Ho VC, Griffiths CE, Ellis CN, Gupta AK, McCuaig CC, Nickoloff BJ, *et al.* Intralesional cyclosporine in the treatment of psoriasis. A clinical, immunologic, and pharmacokinetic study. *J Am Acad Dermatol* 1990;**22**:94–100.	Intralesional cyclosporin
Kokelj F, Torsello P, Plozzer C. Calcipotriol improves the efficacy of cyclosporine in the treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 1998;**10**:143–6.	Non-randomised study
Levell NJ, Shuster S, Munro CS, Friedmann PS. Remission of ordinary psoriasis following a short clearance course of cyclosporin. *Acta Derm Venereol* 1995;**75**:65–9.	Mild-to-moderate psoriasis
Mrowietz U, Christophers E. Low-dose ciclosporin A (Sandimmun®) in psoriasis: a multicenter dose-finding study. *Z Hautkr* 1991;**66**:25–9.	Same data as Christophers *et al.,* 1992[41]
Nakayama J, Hori Y, Nakagawa H, Ishibashi Y, Horikoshi T, Ozawa A, *et al.* Comparison of two therapeutic regimens, continuous monotherapy and intermittent therapy, for long-term maintenance of remission of psoriasis with cyclosporin A. *Eur J Dermatol* 1996;**6**:341–3.	Data contained in Ozawa *et al.*, 1999[38]
Petronic Rosic VM, Marinkovic JM, Cvijetic OB. Intralesional cyclosporine versus dithranol in the treatment of plaque-type psoriasis. *Eur J Dermatol* 1997;**7**:492–6.	Intralesional cyclosporin
Schulze HJ. Comparative trial of Sandimmune and etretinate for plaque-type psoriasis. *Z Hautkr* 1991;**66**:33–8.	Data are a subset of Mahrle *et al.*, 1995[46]
Timonen P, Friend D, Abeywickrama K, Laburte C, Von Graffenried B, Feutren G. Efficacy of low-dose cyclosporin A in psoriasis: results of dose-finding studies. *Br J Dermatol* 1990;**122**:33–9.	Non-randomised study
Wanqing L, Zhigang L, Wei H. Clinical study of cyclosporin A for psoriasis in China. *Ann Dermatol* 1995;**7**:313–17.	Non-randomised study

Appendix 2

Retinoid studies excluded

Study	Reason for exclusion
Bayerl C. Treatment of psoriasis vulgaris with etretinate versus cyclosporin A. Report on a study. *Aktuel Dermatol* 1992;**18**:27–31.	Data are a subset of Mahrle *et al*., 1995[46]
Bergner T, Ruzicka T, Przybilla B. Combined acitretin–UV-treatment for severe psoriasis. *Z Hautkr* 1991;**66**(Suppl 4):44–8.	Same data as Ruzicka *et al*., 1990[60]
Bischoff R, De Jong EM, Rulo HF, Sendagorta E, Czarnetzki BM, Van de Kerkhof PC. Topical application of 13-*cis*-retinoic acid in the treatment of chronic plaque psoriasis. *Clin Exp Dermatol* 1992;**17**:9–12.	Topical retinoic acid
Bjerke JR, Geiger JM. Acitretin versus etretinate in severe psoriasis. A double-blind randomized Nordic multicenter study in 168 patients. *Acta Derm Venereol Suppl (Stockh)* 1989;**146**:206–7.	Data published in full later
Darouti E, Rubaie A. Psoriasis treatment with RePUVA in the United Arab Emirates. *Int J Dermatol* 1988;**27**:593–5.	Non-randomised study
Goerz G, Orfanos CE. Systemic treatment of psoriasis with a new aromatic retinoid. Preliminary evaluation of a multicenter controlled study in the Federal Republic of Germany. *Dermatologica* 1978;**157**:138–44.	Non-randomised study
Gollnick H, Orfanos CE. Clinico-therapeutic index and dosimetry of oral treatment with aromatic retinoid. A comparison of different dosages. *Hautarzt* 1983;**34**:605–11.	Large case series
Gruca S, Jakubowicz K. Psoriasis treatment with aromatic derivatives of retinoids (Tigason) in a double blind trial. *Przegl Dermatol* 1984;**71**:273–8.	Same data as Jakubowicz *et al*., 1987[63]
Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ. Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol* 1989;**20**:1088–93.	Data published in full later
Koh WS, Youn JI. Comparison of PUVA and retinoid–PUVA in the treatment of psoriasis in Korean patients. *Ann Dermatol* 1995;**7**:112–15.	Non-randomised study
Lane Brown M. 5-Methoxy psoralen, etretinate, and UVA for psoriasis. *Int J Dermatol* 1987;**26**:655–9.	Non-randomised study
Langner A, Stapor V, Wolska H, Verjans H, Elzerman JR. Combined treatment of chronic plaque psoriasis with etretinate and topical 1,25-dihydroxyvitamin D-3 [4]. *J Dermatol Treatment* 1995;**6**:53.	Non-randomised study
Lawrence CM, Marks J, Shuster S. Addition of retinoids to PUVA for psoriasis [letter]. *Lancet* 1983;**1**:706.	Data published in full later
Murray HE, Anhalt AW, Lessard R, Schacter RK, Ross JB, Stewart WD, *et al*. A 12-month treatment of severe psoriasis with acitretin: results of a Canadian open multicenter study. *J Am Acad Dermatol* 1991;**24**:598–602.	Non-randomised study
Orfanos CE, Mahrle G, Goerz G, Happle R, Hofbauer M, Landes E, *et al.* Laboratory investigations in patients with generalized psoriasis under oral retinoid treatment. A multicenter study of computerized data. *Dermatologica* 1979;**159**:62–70.	Large case series
Park YK, Hann SK, Hong KT. A clinical evaluation of the effects of combination photochemotherapy in the treatment of psoriasis with etretinate and PUVA. *Korean J Dermatol* 1987;**25**:460–6.	Non-randomised study
Rosinska D, Wolska H, Konca I. [Results of Tigason treatment of children with severe forms of psoriasis and ichthyosis.] *Przegl Dermatol* 1987;**74**:344–51.	Non-randomised study
Schulze HJ. Comparative trial of Sandimmune and etretinate for plaque-type psoriasis. *Z Hautkr* 1991;**66**:33–8.	Data are a subset of Mahrle *et al.,* 1995[46]

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Study	Reason for exclusion
Snodgrass Cowart V. Etretinate therapy improves psoriasis but elevates serum lipids. *JAMA* 1982;**247**:2647–8.	Editorial
Sonnichsen N, Harnack K, Barth J, Heilmann S, Jager K, Metz D, *et al*. Psoriasis therapy with the aromatic retinoid Ro 10-9359 (Tigason). *Z Hautkr* 1983;**58**:1257–67.	Non-randomised study
Stern RS, Fitzgerald E, Ellis CN, Lowe N, Goldfarb MT, Baughman RD. The safety of etretinate as long-term therapy for psoriasis: results of the etretinate follow-up study. *J Am Acad Dermatol* 1995;**33**:44–52.	Non-randomised study
Takashima A, Sunohara A, Matsunami E, Mizuno N. Comparison of therapeutic efficacy of topical PUVA, oral etretinate, and combined PUVA and etretinate for the treatment of psoriasis and development of PUVA lentigines and antinuclear antibodies. *J Dermatol* 1988;**15**:473–9.	Non-randomised study
Wanqing L, Zhigang L, Wei H. Clinical study of cyclosporin A for psoriasis in China. *Ann Dermatol* 1995;**7**:313–17.	Non-randomised study
Weinstein GD, Krueger GG, Lowe NJ, Duvic M, Friedman D, Jegasothy BV, *et al*. Tazarotene gel, a new retinoid for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy and duration of therapeutic effect. *J Am Acad Dermatol* 1997;**37**:85–92.	Mild-to-moderate psoriasis

Appendix 3

Methotrexate studies excluded

Study	Reason for exclusion
Liang GS, Kerdel FA. Combination therapy and the use of an initial dose of intramuscular methotrexate in patients hospitalized for psoriasis. *J Dermatol Treatment* 1995;**6**:73–6.	Flawed study design: unblinded comparison of non-standard methotrexate regimen vs no intervention (large single initial intramuscular dose of methotrexate or no injection), used in conjunction with a variety of other systemic and topical therapies in patients with a wide range of psoriasis types (guttate, plaque, erythrodermic or pustular)
Willkens RF, Williams JH, Ward JR, Egger MJ, Reading JC, Clements PJ, *et al.* Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheumatism* 1984;**27**:376–81.	Results not evaluable: study designed to examine efficacy of methotrexate in psoriatic arthritis rather than psoriasis, no baseline data on psoriasis severity included, minimal assessment of changes in psoriasis severity

Appendix 4

Phototherapy and photochemotherapy studies excluded

Study	Reason for exclusion
Bedi TR. A comparative evaluation of modified Goeckerman regimen and oral psoralens plus phototherapy in psoriasis. *Indian J Dermatol Venereol Leprol* 1979;**45**:181–5.	Non-randomised allocation
Berne B, Blom I, Spangberg S. Enhanced response of psoriasis to UVB therapy after pretreatment with a lubricating base. A single-blind controlled study. *Acta Derm Venereol* 1990;**70**:474–7.	Target lesions evaluated
Boer J, Hermans J, Schothorst AA, Suurmond D. Comparison of phototherapy (UV-B) and photochemotherapy (PUVA) for clearing and maintenance therapy of psoriasis. *Arch Dermatol* 1984;**120**:52–7.	Non-randomised allocation
Calzavara Pinton PG, Ortel B, Honigsmann H, Zane C, De Panfilis G. Safety and effectiveness of an aggressive and individualized bath-PUVA regimen in the treatment of psoriasis. *Dermatology* 1994;**189**:256–9.	Non-randomised allocation
Calzavara Pinton PG, Rastelli M, Zane C, Boccaletti V, De Panfilis G. 'Bath-PUVA': a real advance in the photochemotherapy of chronic plaque-type psoriasis. *G Ital Dermatol Venereol* 1994;**129**:227–32.	Non-randomised allocation
Coven TR, Burack LH, Gilleaudeau R, Keogh M, Ozawa M, Krueger JG. Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. *Arch Dermatol* 1997;**133**:1514–22.	Non-randomised allocation
Danno K, Horio T, Ozaki M, Imamura S. Topical 8-methoxypsoralen photochemotherapy of psoriasis: a clinical study. *Br J Dermatol* 1983;**108**:519–24.	Left/right comparison
Darouti E, Rubaie A. Psoriasis treatment with RePUVA in the United Arab Emirates. *Int J Dermatol* 1988;**27**:593–5.	Non-randomised allocation
Diette KM, Momtaz TK, Stern RS, Arndt KA, Parrish JA. Psoralens and UV-A and UV-B twice weekly for the treatment of psoriasis. *Arch Dermatol* 1984;**120**:1169–73.	Non-randomised allocation
Dubertret L, Averbeck D, Bisagni E. Experimental bases and primary trials of photochemotherapy of psoriasis by a non-cancerigenic monofunctional furocoumarin, 3-carbethoxypsoralen. *C R Seances Acad Sci D* 1979;**288**:975–7.	Animal study
Dubertret L, Averbeck D, Zajdela F, Bisagni E, Moustacchi E, Touraine R, *et al.* Photochemotherapy (PUVA) of psoriasis using 3-carbethoxypsoralen, a non-carcinogenic compound in mice. *Br J Dermatol* 1979;**101**:379–89.	Animal study
Eells LD, Wolff JM, Garloff J, Eaglstein WH. Comparison of suberythemogenic and maximally aggressive ultraviolet B therapy for psoriasis. *J Am Acad Dermatol* 1984;**11**:105–10.	Target lesions evaluated
Elbracht C, Landes E. [Study on the efficacy of a combined treatment of psoriasis with dithranol and UV-B (selective ultraviolet-phototherapy).] *Z Hautkr* 1983;**58**:387–97.	Non-randomised allocation
Fischer T. Comparative treatment of psoriasis with UV-light, trioxsalen plus UV-light, and coal tar plus UV-light. *Acta Derm Venereol* 1977;**57**:345–50.	Non-randomised allocation
Fotiades J, Lim HW, Jiang SB, Soter NA, Sanchez M, Moy J. Efficacy of ultraviolet B phototherapy for psoriasis in patients infected with human immunodeficiency virus. *Photodermatol Photoimmunol Photomed* 1995;**11**:107–11.	Non-randomised allocation
Galosi A, Dorn M, Przybilla B. [A new UV-B irradiation unit. Experiences with psoriasis vulgaris with low dosage UV-B irradiation and local cignoline use.] *Z Hautkr* 1985;**60**: 1929–30,1935–6,1939.	

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Study	Reason for exclusion
George SA, Bilsland DJ, Wainwright NJ, Ferguson J. Failure of coconut oil to accelerate psoriasis clearance in narrow-band UVB phototherapy or photochemotherapy. *Br J Dermatol* 1993;**128**:301–5.	Non-randomised allocation
Gould PW, Wilson L. Psoriasis treated with clobetasol propionate and photochemotherapy. *Br J Dermatol* 1978;**98**:133–6.	Left/right comparison
Grupper C, Berretti B. Treatment of psoriasis by oral PUVA therapy combined with aromatic retinoid (Ro 10-9359; Tigason®). *Dermatologica* 1981;**162**:404–13.	Non-randomised allocation
Hofmann C, Neiss A, Plewig G, Braun Falco O. [Oral 8-methoxypsoralen–UVA (PUVA) therapy in psoriasis: comparison of 3 treatment protocols.] *Hautarzt* 1980;**31**:315–23.	Non-randomised allocation
Honigsmann H, Fritsch P, Jaschke E. [UV-therapy of psoriasis. Half-side comparison between oral photochemotherapy (PUVA) and selective UV-phototherapy (SUP).] *Z Hautkr* 1977;**52**:1078–82.	Non-randomised allocation
Kar PK, Jha PK, Snehi PS. Evaluation of psoralen with solar ultraviolet light (Puvasol) and adjunctive topical tar therapy in psoriasis. *J Indian Med Assoc* 1994;**92**:120–1.	Non-randomised allocation
Karvonen J, Kokkonoen EL, Ruotsalainen E. 311nm lamps in the treatment of psoriasis in the Ingram regimen. *Acta Derm Venereol (Stockh)* 1989;**69**:82–5.	Non-randomised allocation
Kenicer KJA, Lakshmipathi T, Addo HA, Johnson BE, Frain-Bell W. An assessment of the effect of photochemotherapy (PUVA) and UVB phototherapy in the treatment of psoriasis. *Br J Dermatol* 1981;**105**:629–39.	Non-randomised allocation
Kokelj F, Plozzer C, Guadagnini A. Topical tacalcitol reduces the total UVB dosage in the treatment of psoriasis vulgaris. *J Dermatol Treatment* 1996;**7**:265–6.	Non-randomised allocation, target lesions only
Lane Brown M. 5-Methoxy psoralen, etretinate, and UVA for psoriasis. *Int J Dermatol* 1987;**26**:655–9.	Non-randomised allocation
Langner A, Wolska H, Kowalski J, Duralska H, Murawska E. Photochemotherapy (PUVA) and psoriasis: comparison of 8-MOP and 8-MOP/5-MOP. *Int J Dermatol* 1976;**15**:688–9.	Non-randomised allocation
Ledo A. A double-blind comparison of PUVA therapy combined with either bazalin or betamethasone dipropionate in the treatment of psoriasis. *Curr Ther Res Clin Exp* 1981;**29**:493–502.	Left/right comparison
Lowe NJ, Weingarten D, Bourget T, Moy LS. PUVA therapy for psoriasis: comparison of oral and bath-water delivery of 8-methoxypsoralen. *J Am Acad Dermatol* 1986;**14**(5 Pt 1):754–60.	Non-randomised allocation
Melski JW, Tanenbaum L, Parrish JA, Fitzpatrick TB, Bleich H, 28 participating investigators. Oral methoxsalen photochemotherapy for the treatment of psoriasis: a co-operative clinical trial. *J Invest Dermatol* 1977;**68**:328–55.	Partially randomised allocation
Momtaz TK, Parrish JA. Combination of psoralens and ultraviolet A and ultraviolet B in the treatment of psoriasis vulgaris: a bilateral comparison study. *J Am Acad Dermatol* 1984;**10**:481–6.	Non-randomised allocation
Nowakowski H, Jakubowicz K. Treatment of psoriasis with psoralen derivatives and long-wave ultraviolet radiation (PUVA method). II. Durability of therapeutic results and recurrences. Comparison of Oxsoralen and Beroxan. *Przegl Dermatol* 1979;**66**:81–6.	Non-randomised allocation
Ortel B, Perl S, Kinaciyan T, Calzavara Pinton PG, Honigsmann H. Comparison of narrow-band (311 nm) UVB and broad-band UVA after oral or bath-water 8-methoxypsoralen in the treatment of psoriasis. *J Am Acad Dermatol* 1993;**29**(5 Pt 1):736–40.	Non-randomised allocation
Park YK, Whang KC. A study of combined methotrexate–UVB therapy for the treatment of psoriasis. *Korean J Dermatol* 1985;**23**:456–61.	Non-randomised allocation
Paul BS, Momtaz K, Stern RS, Arndt KA, Parrish JA. Combined methotrexate–ultraviolet B therapy in the treatment of psoriasis. *J Am Acad Dermatol* 1982;**7**:758–62.	Non-randomised allocation
Petzelbauer P, Honigsmann H, Langer K, Anegg B, Strohal R, Tanew A, *et al*. Cyclosporin A in combination with photochemotherapy (PUVA) in the treatment of psoriasis. *Br J Dermatol* 1990;**123**:641–7.	Non-randomised allocation

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Study	Reason for exclusion
Pullmann H, Zingheim M, Steigleder GK, Orfanos CE. [PUVA and anthraline therapy of psoriasis, a clinical, histological and autoradiographic comparison.] *Z Hautkr* 1976;**51**:861–71.	Non-randomised allocation
Roenigk HH. Photochemotherapy for psoriasis. A clinical co-operative study of PUVA-48 and PUVA-64. *Arch Dermatol* 1979;**115**:576–9.	Non-randomised allocation
Sonnichsen N, Harnack K, Barth J, Heilmann S, Jager K, Metz D, *et al*. [Psoriasis therapy with the aromatic retinoid Ro 10-9359 (Tigason).] *Z Hautkr* 1983;**58**:1257–67.	Non-randomised allocation
Speight EL, Farr PM. Calcipotriol improves the response of psoriasis to PUVA. *Br J Dermatol* 1994;**130**:79–82.	Left/right comparison
Swanbeck G, Thyresson Hok M, Bredberg A, Lambert B. Treatment of psoriasis with oral psoralens and longwave ultraviolet light. Therapeutic results and cytogenetic hazards. *Acta Derm Venereol* 1975;**55**:367–76.	Non-randomised allocation
Takashima A, Sunohara A, Mizuno N. Comparison of the relative therapeutic efficacy of 7-methyl pyridopsoralen and 8-methoxypsoralen in photochemotherapy in psoriasis treatment. *J Dermatol* 1988;**15**:195–201.	Target lesions evaluated
Talwalkar PG, Gadgil RG, Oberai C, Parekh VD. Evaluation of 8-methoxypsoralen and solar light (Puvasol) in psoriasis. *Indian J Dermatol Venereol Leprol* 1981;**47**:17–20.	Non-randomised allocation
Wainwright NJ, Dawe RS, Ferguson J. Narrowband ultraviolet B (TL01) phototherapy for psoriasis: which incremental regimen? *Br J Dermatol* 1998;**139**:410–14.	Target lesions evaluated
Wolff KW, Fitzpatrick TB, Parrish JA, Gschnait F, Gilchrest B, Honigsmann H, *et al*. Photochemotherapy for psoriasis with orally administered methoxsalen. *Arch Dermatol* 1976;**112**:943–50.	Non-randomised allocation
Zhang GW. [Treatment of psoriasis by photochemotherapy: a comparison between the photosensitizing capsule of Angelica dahurica and 8-MOP.] *Chung Hua I Hsueh Tsa Chih* 1983;**63**:16–19.	Non-randomised allocation

Appendix 5

Fumaric acid ester studies excluded

Study	Reason for exclusion
Nugteren Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaarzuurtherapie tegen psoriasis; een dubbelblind, placebo-gecontroleerd onderzoek. *Ned Tijdschr Geneeskd* 1990;**134**:2387–91.	Duplicate report of Nugteren Huying *et al.*, 1990[172]
Peeters AJ, Dijkmans BAC, Van der Schroeff JG. Favourable effect of fumaric acid treatment in psoriatic arthritis. *Ned Tijdschr Geneeskd* 1992;**136**:2428–31.	Treatment of psoriatic arthritis rather than psoriasis

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We look forward to hearing from you.

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