Treatment pathways and economic analysis of treatment for severe psoriasis

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Abstract

Psoriasis is a chronic skin disease that affects up to 2% of the UK population. The clinical presentation ranges from mild disease to extensive, severe disease that causes considerable discomfort and distress. Severe disease usually requires photochemotherapy or systemic treatment. Information about the effectiveness, safety and costs of the different treatments is required to enable dermatologists to formulate evidence-based treatment guidelines. Systematic reviews of the four main treatment modalities for moderate-severe psoriasis (cyclosporin, methotrexate, systemic retinoids and photochemotherapy) were performed. Randomised controlled trials were located systematically by electronic searching, hand searching and personal communications. Data on trial characteristics and outcomes were extracted and tabulated. Where possible data were pooled to give summary effect sizes as odds ratios, rate differences or numbers needed to treat (NNTs). Firm RCT evidence of efficacy was found for cyclosporin, oral retinoids, particularly in combination with PUVA, phototherapy, photochemotherapy and for combinations of topical calcipotriol or steroids with phototherapy. The corresponding NNTs were low, indicating high levels of efficacy. RCT evidence of efficacy is lacking for methotrexate. Two observational studies of patients attending the Psoriasis Specialty Clinic were performed. The first was a cross-sectional study that used data in existing disease assessment documentation to identify the characteristics of a group of 256 patients. The second was a longitudinal study that followed the treatment pathways of 166 patients in the first group. These studies confirmed that this group of patients and their treatments were comparable with those described in the literature. An economic analysis was performed, using a previously published decision-analytic model, to compare four treatment strategies for severe psoriasis from the health service perspective. The results (cost-effectiveness ratios) showed that methotrexate was the most cost-effective primary treatment followed by cyclosporin, acitretin and PUVA. The rank order was not sensitive to changes in response rates. Modifications to the decision analytic model are proposed including a wider array of pathways and an allowance for adverse effects of treatment. Future analyses should include narrowband UVB alone as a primary treatment.

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Publications arising from these studies

1. Griffths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC. A systematic review of treatments for severe psoriasis. Health Technol Assess 2000; 4 (40) (Executive summary shown at Appendix 3)

2. Clark CM, Chalmers RJG, Rowe PH, Li Wan Po A, Williams HC and Griffiths CEM. A systematic review of therapies for severe psoriasis. (poster) Br J Dermatol 2001; 145 (Suppl 59): 42. (Appendix 4).

Chapter 1

Evidence-Based Medicine

Summary

This chapter reviews the background to the development of evidence-based medicine (EBM) and describes the methodological 'tools' which are used to gather and synthesise the evidence. The implementation of EBM is considered briefly.

1.1 Evidence-based Medicine: Background

Although the philosophical origins of evidence-based medicine (EBM) date back for many decades, the current drive for EBM in the NHS was triggered by the combination of rising costs and evidence of wide variations in medical practice. (Weatherall 1994) There was also mounting concern that many interventions had little basis other than tradition.

In January 1996 the NHS Executive stated its commitment to ensuring

> "that decisions about the provision and delivery of clinical services are driven increasingly by evidence of clinical and cost-effectiveness, coupled with systematic assessment of actual health outcomes". (NHS Executive 1996a)

In the same month Sackett and colleagues described EBM as, "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients". (Sackett 1996) It follows from both statements that the practice of EBM involves two critical steps, firstly the identification of "evidence" and, secondly, its application.

This chapter reviews the methodological tools which are used to identify and synthesise evidence and the common approaches to implementation of EBM.

1.2 The tools of evidence-based medicine

For any therapeutic intervention there exists a body of experience in the scientific literature and in the memories of clinicians. This, therefore, is the 'evidence' which has to be systematically extracted and analysed. A critical step in this process is to devise a decision-analytic model which accurately describes the options open to a clinician and the possible decision pathways. In order to do this, the raw evidence has first to be located, sifted, analysed and synthesised to ensure that the final model is based on reliable material of suitable quality. The techniques of systematic review

and economic analysis are employed to analyse and synthesise the evidence. Only when this stage is complete can the evidence be translated into meaningful therapeutic guidelines. Guidelines derived through a less rigorous process cannot really be said to merit the description 'evidence-based'.

1.2.1 Decision analysis

Decision analysis is a systematic, quantitative technique for structuring the decision-making process. It has been described and recommended as a means of helping clinicians to make decisions about the care of individual patients. (Weinstein 1980, Sox 1988) However it can also be used to analyse treatment strategies for groups of patients and to form the basis for cost-effectiveness analysis. It has even been used to analyse the cost-effectiveness of medical research itself. (Drummond 1992) It is particularly helpful when a decision is complex and involves an element of uncertainty.

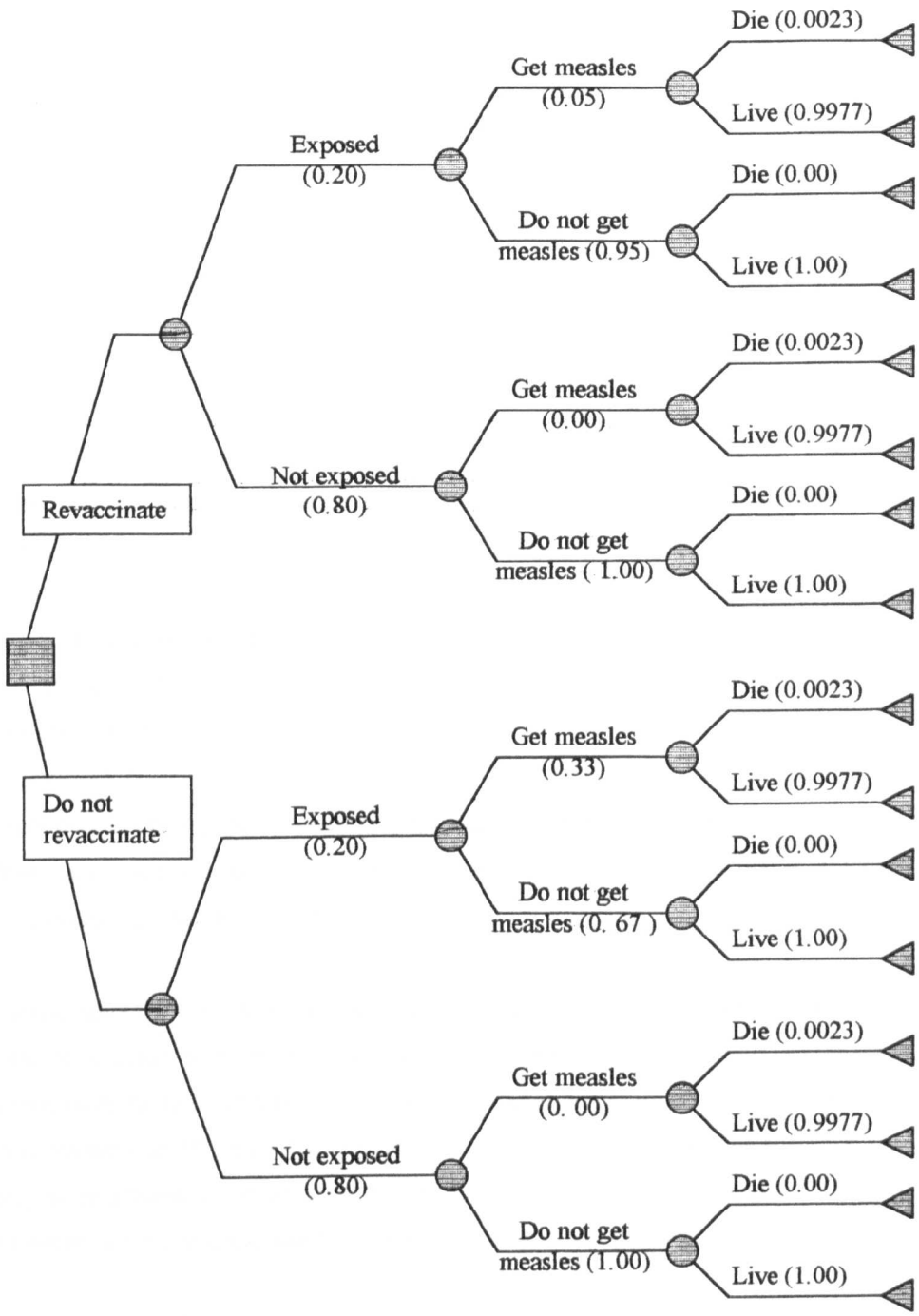
There are five steps in a decision analysis (Petitti 1994):

- identification of the problem
- structuring of the problem (using a decision-analytic model, 'decision tree')
- gathering information about uncertainties and outcomes
- analysis of the tree
- sensitivity analysis

Clear identification of the problem is the critical first step so that the resulting tree has a recognisable focus, timing, horizon and perspective. A specific starting point must be identified along with a realistic time horizon.

The decision tree is a flow diagram showing decisions and outcomes, in time sequence, moving from left to right. The tree must clearly distinguish between choices (which are under the decision-maker's control) and chance events (which are beyond the decision-maker's control). It must also distinguish between outcomes (which describe facts, states of being) and outcome valuations (utility values). In order to represent these entities in a decision tree three types of "node" are used. They are; decision nodes (square), chance nodes (round) and outcome nodes (triangular). Two basic rules must be obeyed when constructing the tree; firstly, the branches from a node must be exhaustive and mutually exclusive and, secondly, the sum of probabilities in each branch must be equal to one. (figure 1.1 shows an example of a decision tree)

Figure 1.1: Measles revaccination decision analysis – decision tree format



Gathering the information to fill in the decision tree is the next step. Probabilities must be determined for each chance event and utility values assigned to outcomes. Probabilities are derived from systematic review of the literature (see below), primary data collection or consultation with experts. By convention, death is given a value of zero and life (survival) is given a value of one. Values for intermediate states, such as survival with a disability are determined by a standardised wager technique. (Jefferson 1996) This involves asking a patient to choose between two hypothetical options, for example;

- option A: no risk of death but the certainty of a degree of disability
- option B: a 0.5 chance of complete cure but also a 0.5 chance of death.

Most patients will choose option A. The wager is then reformulated with a reduced chance of death. This process is repeated until the patient has difficulty choosing between the two options. This point will be associated with a value for the chance of complete cure (e.g. 0.95) and a value for the chance of death (0.05). This is described as "the level of indifference".

The decision tree is analysed by a process of "folding back" and averaging. This can be done either with or without utility values. An example of a tree using probabilities alone is shown in figure 1.1, which describes the probabilities of death or survival depending on whether subjects are re-vaccinated or not. "Folding back" refers to the process of multiplying together all the probabilities associated with each outcome. This is more easily seen if the information on the tree is set out as a spreadsheet (see table1.1). "Averaging" refers to the summation of the products of the rows that lead to the same outcome.

This example only has two outcomes (*die* or *don't die (live)*) however, for a problem with intermediate outcomes, the utility value of each outcome may be included. The option with the highest utility value can then be computed.

Finally, the robustness of the model is tested by means of sensitivity analysis. In this process the values of one or more key parameters are varied to test the effect on the final result. In the measles re-vaccination example, the probability of exposure to measles was estimated to be 20% although in practice it varies between 1% and 40%. A sensitivity analysis would examine the effects of substituting values between 1 and 40 on the number of lives saved by re-vaccination. This identifies weaknesses in the model and may be used to guide future research.

Table 1.1 Measles Re-vaccination Decision Analysis - Spreadsheet Format

Sum for deaths (sum of products for lines 1,3,5 & 7) = 0.000152

Difference between revaccination and no vaccination = 0.000152 - 0.000023 = 0.000129

Difference as events per 100,000 = 12.9 deaths

(After Pettiti 1994)

1.2.2 Systematic review

The purpose of a systematic review is to summarise and present both published and (if possible) unpublished data in a comprehensive form. This information may be used as the basis for a meta-analysis or may be used directly to estimate a probability for cost-effectiveness analysis. The process of systematic reviewing involves the location, appraisal and synthesis of evidence from scientific studies in order to provide informative empirical answers to scientific research questions. (NHS CRD 1996) A systematic review differs from a traditional review paper in that the methodology is explicit, the review attempts to capture all relevant data and the analysis should be free from bias.

There are eight steps in the preparation of a systematic review: (Lefebvre 1994)

- statement of the objectives of the review
- definition of the eligibility criteria
- search for eligible studies (information retrieval)
- assessment of the quality of each study
- application of the eligibility criteria and justification of any exclusions
- analysis of the results of the eligible studies (data extraction)
- data synthesis
- preparation of the report

It is recommended that the whole review process should be planned in advance and recorded as a written protocol. (Meade 1998) In this way it should be possible to ensure that the methods are driven solely by the aims and bias is avoided. The protocol should specify the question(s) to be answered, the strategies for information retrieval and data extraction, the screening criteria and the means by which the data will be synthesised. The protocol should provide a framework to ensure that the research question is answered rather than specifying narrow, untested selection criteria which may exclude all the available studies.

It has been suggested that each review question should describe three elements, (1) the participants (subjects) in the primary studies and their disease status, (2) the intervention under consideration and (3) the outcomes which evaluate the success of the intervention. (NHS CRD 1996)

Before the search for suitable studies is started, eligibility criteria must be defined. Most systematic reviews are based on randomized controlled trials (RCTs) as this methodology is most likely to distinguish reliably between the effects of an intervention and the effects of bias or chance. If sufficient RCTs are not available then the next best quality evidence must be used. Table 1.2 shows the conventionally accepted hierarchy of evidence.

Table 1.2: Hierarchy of Evidence

(Eccles 1998)

It is important that the information retrieval process is scientifically defensible and free of bias. It follows that all the available information needs to be identified. In practice it may not be possible to locate unpublished information and there may be considerable difficulties in trying to retrieve information published in foreign languages. The reviewer needs to be aware of the phenomenon of publication bias. This is the bias introduced because studies with positive results are more likely to be published than those with negative results. Thus, even if a comprehensive search is successfully performed, the results may not represent all the work that has been done in that field. Electronic databases may identify as few as 50% of the relevant studies and so the information retrieval strategy must go beyond electronic searching alone. The ideal approach is summarised in Table 1.3

Table 1.3: Steps for comprehensive retrieval of published information on a specific topic

(After Petitti 1994)

The computerised search must be designed with care. Most systematic reviews set out to retrieve randomized controlled trials, however, until recently bibliographic databases, such as Medline and Embase were inadequately designed for this purpose and lacked suitable indexing terms. (Lefebvre 1994) In order to maximize the chances of identifying all the available RCTs optimally-sensitive search strategies (OSSS) have been devised. (Dickersin 1994, NHS CRD 1996) The search strategy recommended by the NHS Centre for Reviews and Dissemination is shown in Appendix 1.

Once all the relevant articles have been assembled, they must be screened for quality and eligibility using the criteria established at the outset. Some general criteria for assessing the quality of RCTs have been identified (see Table 1.4) but other specific criteria relating to the question under investigation may need to be added. After screening the remaining papers can then be used for data extraction. It is recommended that data-extraction forms be prepared in advance so as to minimise bias. (Meade 1998) This process should involve extensive testing and consultation with experts in the field to ensure that critical elements of data are not overlooked. Data extraction forms vary considerably, depending on the area of investigation. An example is shown at Appendix 2.

Table 1.4: Generic criteria for assessment of randomised controlled trials

1	Was the assignment to the treatment groups really random?
2	Was the randomisation of the participants blinded?
3	Was relatively complete follow-up achieved?
4	Were the outcomes of people who withdrew described and included in the analysis?
5	Were those assessing outcomes blind to treatment allocation?
6	Were the control and treatment groups comparable at entry?
7	Were the groups treated identically other than for the named intervention?

(CRD Report Number 4, 1996)

The results of the primary studies are then drawn together to provide a broad, qualitative overview. It may also be possible to undertake a quantitative synthesis using the techniques of meta-analysis. In this way a summary measure of effect size can be derived from pooled data. As with any statistical method, it is important that the most appropriate method is selected for the data in question. (This will be discussed in more detail in Chapter 6)

The final report of a systematic review should include a clear description of the purpose, methods, results and implications of the review.

1.2.3 Economic analysis

Several different types of economic evaluation are possible but some elements are common to all. Generally, two or more interventions are considered and the inputs (resources) needed to deliver it are compared with the outputs (results, effects). It follows, therefore, that cost-of-illness (COI) studies, which consider inputs only, are not considered to be true economic evaluations. Different types of economic evaluation measure inputs and outputs in different units. The characteristics of the four main types of economic analysis are summarised in Table 1.5.

Cost-effectiveness analysis (CEA)

It can be seen from Table 1.5 that CEA compares the outcome of decision options in terms of cost per unit of effectiveness. In practice, this type of analysis is most widely used in healthcare and so this will described.

Cost-effectiveness analysis contributes to and builds on to decision analysis, using a decision tree as its starting point. The following additional steps are necessary:

- Definition of the perspective of the analysis
- Identification of cost data
- Analysis of cost data
- Sensitivity analysis

The perspective of a CEA must always be stated explicitly as this will determine which costs are included. For example, an analysis from a provider perspective would include direct and indirect costs of providing a treatment, whereas an analysis of the same treatment from the patient perspective might include travelling expenses for clinic visits and loss of income.

Cost data must be carefully researched and the difference between costs and charges must be clearly understood. For example, it might cost a hospital laboratory £5.00 to carry out a test (including reagents, labour and overheads) but the hospital might charge £10.00 to perform the test for a private clinic. In this case the cost to the hospital is £5.00 but to the private clinic the cost is £10.00. The figure used in an economic evaluation will depend on its perspective. In general, cost data are either taken from administrative sources or are gathered *de novo* in suitable observational studies.

Cost data can be added to the decision tree so that the net cost of each of the decision options can be calculated.

Sensitivity analysis is an essential part of a CEA as it allows the researcher to test the effects of the assumptions that have been made. It may also help to identify cost elements which are critical to the model and which may be liable to change. An example of this is a study which examined the cost-effectiveness analysis of screening for and eradication of Helicobacter pylori. (Briggs 1996) In this study the authors examined the effects of varying 18 different parameters on their model. They were able to show that the cost of antisecretory medication had a more significant effect on the payback period than all other factors, including the accuracy of endoscopy and the effectiveness of eradication treatment.

1.3 Implementation of EBM

Sackett and colleagues explained how it should be possible to apply epidemiological and biostatistical evidence to improve the clinical care of patients in 1991. (Sackett 1991) Since that time this group has lead the field in developing techniques that clinicians can use to make their practice 'evidence-based'. (Sackett 2000).

In 1996 the NHS Executive issued guidance which called on chief executives to ensure that sound information was available, including decision-support systems, in order to improve clinical effectiveness. (NHS Executive 1996a) This was rapidly followed by a document which described how clinical guidelines should be developed and used in clinical practice. (NHS Executive 1996b)

Understanding of the principles of EBM is gradually spreading through professional communities, and over the next few years it is likely that healthcare providers and consumers will increasingly ask for evidence-based approaches to treatment and care. This is already clearly reflected in the guidelines produced by the National Institute for Clinical Excellence (NICE) which commonly recommend an evidence-based approach to treatment.

Table 1.5: Types of economic evaluation

(After Clark CM 1998)

Chapter 2

Psoriasis and its Treatment

Summary

This chapter reviews the clinical presentation, pathology and epidemiology of psoriasis. Licensed treatments for psoriasis, including phototherapy, are described. Topical treatments are considered briefly and systemic treatments are considered in detail. Unlicensed treatments are mentioned briefly.

2.1 Psoriasis

2.1.1 Clinical presentation

Psoriasis occurs in several different forms. Chronic plaque is the most common and it accounts for more than 90% of cases. (Stern 1997) It is characterised by plaques on the trunk and extensor surfaces of the limbs that are typically well-demarcated, reddened, thickened and covered in silvery scales. They may be small and discrete or large and confluent and the skin may be up to sixteen times thicker than normal skin. (Clark 1999) Patients may also have psoriatic lesions affecting the scalp and in this area thick scales may be a major problem. In some patients, psoriatic lesions occur in the flexures (armpits, groin, infra-mammary area) and in these areas plaques are typically red and inflamed but lack the covering of silvery scale.

Removal of the silvery psoriatic scales causes characteristic "point bleeding" although superficial scales from the surface of plaques are shed freely. In addition, patients complain of itching, extreme dryness of skin and painful cracking and bleeding.

In many patients characteristic changes are seen in nails (both fingers and toes). These include pitting, "oil spots" and onycholysis. Fifteen percent of patients also have a sero-negative arthritis.(Stern 1997)

Guttate psoriasis is so named because lesions are scattered over the skin surface like droplets of liquid spattered from a paintbrush. The individual lesions are small, round, red macules. This form of psoriasis is usually seen in children and adolescents and is often triggered by a streptococcal throat infection

Palmo-plantar pustular psoriasis is a relatively rare condition in which multiple sterile pustules appear on the palms and soles.

Generalised pustular psoriasis and erythrodermic psoriasis are rare but serious conditions which usually require immediate in-patient treatment.

2.1.2 Pathological processes

In earlier times psoriasis was described simply as a hyperproliferative disease in which skin cells were formed more rapidly than usual. In the past 10 years there have been considerable advances in the understanding of the pathological processes that give rise to the clinical manifestations of psoriasis. Although the full picture is still not clear, it seems that T-lymphocytes play a central role. A recent hypothesis suggests that the first step is the presentation of antigens or superantigens, by antigen-presenting cells (APCs) to CD4 helper T lymphocytes in the epidermis. This induces the release of cytokines from both APCs and the T-lymphocytes. The cytokines in turn bring about keratinocyte proliferation and the release of adhesion molecules from endothelial cells. The presence of adhesion molecules allows leucocytes, including skin-homing, memory CD4 T-lymphocytes, to infiltrate the area. These mechanisms may be responsible both for inducing and maintaining psoriatic lesions. (Ortonne 1999)

2.1.3 Epidemiology

Psoriasis affects 1-3% of the general population in Europe. (Farber 1998) The prevalence varies considerably between racial groups for example, rates of 0% have been reported in Samoa and in the South American Andes but 4.8% in Norway and 11.8% in the Arctic Kazach'ye. Genetic factors play a role but environmental factors are also relevant. A child has a 16% risk of developing psoriasis if one parent is affected and a 50% if both parents are affected. (Stern 1997) Factors, which have been shown to precipitate or exacerbate psoriasis, include trauma, infection, hormonal disturbances, sunlight, cigarette-smoking, alcohol and emotional disturbances. (Hunter 1995) Drugs which trigger or exacerbate psoriasis include, ACE inhibitors, beta-blockers, chloroquine and hydroxychloroquine, granulocyte colony stimulating factor (GCSF), gold, interferons, lithium, NSAIDs and tetracyclines. (Lee 1999)

2.2 Pharmacological and ultraviolet light treatments

2.2.1 Topical treatments

For many years topical treatments were the only treatments available and they still represent the mainstay for the majority of patients with mild-moderate psoriasis. Topical treatments include emollients, corticosteroids, vitamin D analogues, dithranol, tar preparations and retinoids. Emollients form the mainstay of topical treatment. Their use reduces scaling and itching. Products that contain keratolytic agents such as salicyclic acid or alphahydroxy acids are helpful in converting rough, scaly or cracked plaques into smooth plaques. Cream formulations are cosmetically more acceptable and are often used for visible areas whereas ointment formulations are useful on large areas of dry skin and for overnight treatment. Zinc oxide (in Lassar's paste) is used to deliver dithranol to psoriatic lesions because of its "non-smudging" property.

Topical corticosteroids classified as 'potent' or 'very potent', such as betamethasone or clobetasol propionate cause flattening of psoriatic plaques and reduce inflammation. Very potent steroids may have a role where the skin is very thick (in conditions such as hyperkeratosis of the palms or soles). (Drug & Therapeutics Bulletin 1996). Prolonged use of steroids may lead to cutaneous atrophy with striae and telangiectasia. The skin of the face and flexures is particularly susceptible to these effects. Occlusive dressings increase the effectiveness of topical steroids but also increase absorption and the chances of local side effects (Stern 1997). Withdrawal of steroids can produce exacerbations of psoriasis. Because of the adverse effects, topical steroids are not recommended for long term or extensive use in the management of psoriasis, although they can play a useful role on a short-term basis. Some clinicians find alternating treatment, using a topical steroid in the daytime and calcipotriol in the evenings, helpful in minimising the side-effects of both treatments (Hunter 1995)

Calcipotriol is a synthetic vitamin D analogue (a $1,25(OH)_2D_3$ analogue) which, when applied topically, inhibits epidermal proliferation without having cytotoxic effects. (Lea 1996) Calcipotriol is odourless and non-staining and is available as cream, ointment and scalp solution. Its effectiveness is similar to that of moderate-high potency steroids. Some patients experience skin irritation with calcipotriol. As the facial skin is particularly susceptible to irritation its use should be avoided for facial psoriasis. (Drug & Therapeutics Bulletin 1996). Small amounts of calcipotriol are absorbed from the skin (Lea 1996) but its effect on calcium homeostasis is 100-200 times weaker than that of calcitriol. (Fogh 1997) Nevertheless, the Summary of Product Characteristics (SPC) recommends that the weekly dose should not exceed 100g of cream or ointment. (BNF 1998) Because of its perceived benefit-to-risk profile calcipotriol is the topical treatment of choice for patients who are treated at home for moderate generalised psoriasis.

Tacalcitol is a newer, synthetic vitamin D analogue ($1,24(OH)_2D_3$) which need only be applied once daily. It has a more marked effect on calcium homeostasis than calcipotriol (Fogh 1997) and dosage is limited to a maximum of 5g per day and two, twelve-week courses per year.

Dithranol (dihydroxyanthrone) has been the mainstay of topical treatment for psoriasis in Europe for many years. In the nineteenth century the use of Goa powder for skin diseases, including psoriasis, was observed in India. (Mahrle 1997) Goa powder is crude chrysarobin and comes from the Araroba tree (*Andira araroba, Leguminosae*). It was applied using a cut lime fruit, which was dipped in the powder and dabbed on the skin. (Martindale 1915) Chrysarobin is a mixture of anthroquinones. During World War I there was shortage of the natural product and the synthetic 1,8-dihydroxy-9-anthrone was introduced into clinical use in Germany in 1916.

Dithranol stains the skin (and also clothing and bath fittings) and may cause serious inflammation or blistering of normal skin or skin in sensitive areas. It is commonly prepared in Lassar's paste so that it can be applied to the affected skin and is unlikely to spread on to healthy skin. For many years dithranol treatment involved application for 12 hours but "short-contact" treatment, in which the application lasts for 30-60 minutes, is now the recommended procedure. (Drug & Therapeutics Bulletin 1996) Dithranol is available in a range of concentrations and it is usual to start with the lowest (0.1%) and increase the concentration every few days up to the maximum (2%) or to the maximum tolerable concentration that produces a therapeutic effect. Dithranol treatment can be used at home but may be practically difficult to manage. It is often delivered at an out-patient "daily dressing" clinic but is, inevitably, a time-consuming treatment.

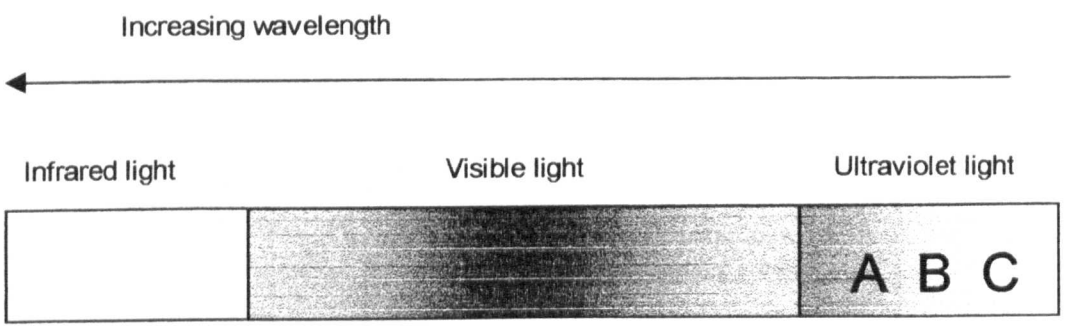
Coal tar has been used for many years and is helpful for patients with mild psoriasis. It has anti-inflammatory and anti-proliferative effects. (Arnold 1997) It is available as crude coal tar, BP preparations such as Coal Tar Paste BP, Calamine and Coal Tar Ointment BP, and is an ingredient in a wide range of proprietary products. Crude coal tar is difficult to use, stains clothing and smells unpleasant to many people. Modern preparations are more acceptable in use. Coal tar is often combined with UVB (as in the Goeckerman regime, see below). This combination is said to increase the effectiveness of the coal tar (Drug & Therapeutics Bulletin 1996) and the coal tar prevents the side effects of maximal erythemogenic UVB monotherapy (Arnold 1997)
Crude coal tar contains a number of carcinogens and percutaneous absorption of mutagens in patients receiving crude coal tar has been demonstrated. (Arnold 1997) This does not appear to translate into a risk for cancer amongst psoriasis patients who receive long-term, intermittent tar treatment. A cohort study of 719 patients failed to show an increase in the number of cancers compared with the general population. (Jones 1985) Nevertheless, in view of the known absorption and the observed risks to workmen who are chronically exposed to industrial tar, long term treatment with concentrations of crude coal tar above 5% should be avoided. (Arnold 1977)

Tazarotene is a topically active retinoid. It is available as a gel formulation (0.05% and 0.1%) for once-daily application. It is licensed for use in mild-moderate psoriasis affecting up to 10% of body surface area. Local irritation is more commonly reported with the higher concentration.

2.2.2 Phototherapy and photochemotherapy

The beneficial effects of sunlight on psoriasis have been known for many years and artificial UV light has been used alone and in combination with photosensitising agents to treat psoriasis. Ultraviolet light comprises the UVA, UVB and UVC bands of the electromagnetic spectrum (see figure 2.1).

Figure 2.1: The electromagnetic spectrum



2.2.2.1 Ultraviolet B therapy

The mechanism of action of UV light in psoriasis treatment is not fully understood. The shorter wavelength UVB is largely absorbed by the epidermis. It is highly energetic and is known to cause a number of photochemical reactions. It is now thought likely that the effects of UVB in psoriasis are due to cytokine modulation, thereby interfering with the pathophysiological processs of the disease (Taylor 1998). 'Broad-band' UVB (wavelength 290-320 nm) has been used widely in combination with coal tar and dithranol (see below). In recent years, work has suggested that 'narrow band' (305-315 nm) UVB treatment on its own may be effective for some patients (Parrish 1981). One of the benefits of narrow band UVB is that the shorter, more erythemogenic wavelengths have been removed, so that the risk of burning is reduced.

The long-term risks of carcinogenesis as a result of UVB treatment are as yet unknown. It is known that UVB is a carcinogen and that male patients undergoing UVB treatment have an

increased risk of developing tumours in genital skin (Stern 1990), but the risk of non-melanoma skin cancer occurring elsewhere is not known. Furthermore, the relative risks of broad band and narrow band UVB treatment are not known. The erythema action spectrum is believed to parallel the carcinogenesis spectrum and, therefore, narrow band UVB should carry a lower risk of tumour induction. However, the absence of erythema may permit larger doses of radiation to be delivered, and this may be also be an important factor.

UVB with coal tar and UVB with dithranol

(UVB) (wavelength 290-320 nm) in combination with coal tar is one of the oldest treatments for moderate-severe psoriasis. In 1925 Goeckerman devised a regime which involves the combined use of crude coal tar and UVB. (Lowe 1997) (Table 2.1) The Goeckerman regime is only suitable for use on an inpatient setting, as it involves 24-hour treatment with tar products. UVB may also be used in combination with dithranol (Ingram 1953) (Table 2.2).

Table 2.1: Goeckerman regime (UVB + tar) - General scheme

STEP	PROCEDURE
1	Apply coal tar (3-5% in yellow soft paraffin) to whole body. Re-apply as necessary to maintain contact between tar and skin
2	After 24 hours clean excess tar off with vegetable oil
3	Give minimal erythematous dose of UVB
4	Remove remaining tar, using soap/shampoo in a warm but not hot bath. Add bath oil to prevent drying of skin
5	Repeat daily for 14-21 days

Table 2.2: Ingram regime (UVB + tar + Dithranol) - General scheme

STEP	PROCEDURE
1	Clean off old paste with nut oil
2	Soak in a tar bath for 20 minutes
3	Descale the lesions with a towel
4	Give a sub-erythematous dose of UVB
5	Apply dithranol in Lassar's Paste accurately to each plaque. Start with a low concentration such as 0.25% and increase gradually through 0.5%, 1%, 2% according to patient's response.
6	Dust with zinc oxide or starch powder
7	"Suit up" with Tubegauze or stockinette where possible. Leave for 12 hours or overnight.
8	Repeat daily if possible for 20-30 days

The main drawbacks of these treatments are the time required, the unpleasant smell of the tar preparations and the skin staining caused by dithranol.

UVB phototherapy is contra-indicated in patients who are taking photo-sensitising medications (eg thiazide diuretics, tetracyclines) and in patients with underlying photosensitive disease (eg systemic lupus erythematosus, polymorphous light eruption). (Tham Siew Nee 1997)

2.2.2.2 Photochemotherapy with oral psoralen and UVA (PUVA)

UVA is less energetic than UVB and penetrates deeper into the skin. PUVA treatment relies on UVA (wavelength 320-400 nm) irradiation of skin which has been primed with suitable photosensitisers, such as psoralens. A number of naturally-occurring psoralens are known to be effective in this way, and in the 1950s oral 8-methoxypsoralen was introduced, (Ortel 1998) but it was not until 1974 that PUVA treatment as it is known today was first described. (Parrish 1974) Once the psoralen is activated by UVA irradiation, a phototoxic reaction takes place, which results in anti-proliferative, anti-inflammatory and immunosuppressive effects. (Lauharanta 1997) The photo-activated psoralens form adducts with pyrimidine bases and cross-links between complementary strands of DNA. As a result, DNA synthesis and epidermal cell division is inhibited. (Hunter 1995)

A critical element of PUVA therapy is ensuring that the psoralen is present in the skin, in suitable concentrations, at the time of irradiation. Oral 8-methoxypsoralen (8MOP) is widely used but other psoralens and alternative presentations have also been tried. (see summary Table 2.3)

Table 2.3: Psoralen summary table

(Table after Lauharanta 1997)

Patients must be selected carefully for PUVA. Prolonged exposure is associated with an increased risk of non-melanoma skin cancer and photo-ageing of the skin and fair-skinned individuals are more susceptible to these effects (Ortel 1998).

2.2.3 Systemic treatments

Systemic treatments are generally reserved for patients whose psoriasis has failed to respond adequately to topical treatments or phototherapy. (Gawkrodger 1997)

Three agents are available (licensed for use) in the UK, they are cyclosporin, methotrexate and acitretin. Their properties and dosing recommendations are reviewed briefly below.

2.2.3.1 Cyclosporin A

Cyclosporin A is a cyclic undecapeptide that was originally isolated from the soil fungus *Tolypocladium inflatum Gams.* It has a molecular weight of 1202.6 Daltons. Cyclosporin has been used for many years as an immunosuppressant in transplant surgery and its effects in psoriasis are thought to be due to its immunomodulatory activity. In psoriasis it has been shown to prevent the proliferation of T-helper cells and cytotoxic lymphocytes, both of which play a part in the pathogenesis of psoriasis. (de Rie 1997)

Cyclosporin is a highly lipophilic molecule, which is effectively insoluble in water. (Wood 1983) For this reason it was first presented as an oral liquid (dissolved in alcohol and olive oil) and as a corn oil-based soft gelatin capsule. It follows that the drug had to be emulsified in vivo before absorption could take place. Both formulations were associated with profound inter- and intra-individual variations in bioavailability. (Mueller 1994, Kahan 1994) Two factors contributed to this, namely, variable absorption and extensive first-pass metabolism. Oral absorption of cyclosporin occurs primarily in the upper small bowel, and is affected by the rate of gastric emptying, the presence of bile, concomitant food intake and gastro-intestinal disease. (Kahan 1989) 25% of the absorbed dose is removed by the liver before it reaches the general circulation. (Kahan 1989) The result of these effects is a mean bioavailability of 30% (range 5-90%). In 1997 a "micro-emulsion preconcentrate" formulation was introduced which, when it comes into contact with water in gastric fluid, forms a stable microemulsion. This formulation does not rely on the presence of bile salts or mechanical agitation and it has been shown to increase mean bioavailability by 30%, to reduce inter- and intra-individual variability and to improve the relationship between dose and blood levels. (Ritschel 1996) 'One-to-one' dose conversion was recommended on the basis that it would make little difference to those who absorbed cyclosporin well, and would improve the response to treatment amongst the 'poor-absorbers'. (Koo 1997)

As cyclosporin is metabolised via cytochrome p450 3A, it interacts with a number of drugs that compete for this pathway (see Table 2.4)

Table 2.4: Drugs that interact with cyclosporin (after Koo 1997)

After oral dosing peak plasma levels are reached at 2-4 hr. The mean plasma half-life is 19 hr (range 8-24 hr). Cyclosporin is extensively metabolised and eliminated mainly in the bile, although small amounts (~ 6%) are eliminated via kidneys. (Kahan 1989)

Cyclosporin use is indicated in patients who have failed to respond adequately to other treatments. This includes topical treatments and, in some cases, other systemic treatments. It also has a place in the treatment of patients with widespread, severe or disabling disease. (Gawkrodger 1997)

Although doses of 8-16 mg/kg/day are common in transplant surgery, the maximum dose recommended for psoriasis is 5mg/kg/day. Opinion differs as to whether dosage should start high and be adjusted downwards or the other way round. (Berth-Jones 1997) Lebwohl and colleagues recommend that severe, inflammatory exacerbations of psoriasis should be treated initially with high doses whereas patients with stable, generalised disease should be started on low doses. (Lebwohl 1998) Doses should be calculated on the basis of ideal body weight (obese patients may

be overdosed if actual body weight is used). The dose should be divided into two equal doses. (Berth-Jones 1997) Once a marked improvement has been achieved, the dose of cyclosporin should be adjusted to the lowest effective dose for maintenance therapy or it should be discontinued. Several authorities advocate the intermittent, rather than continuous, use of cyclosporin. (Berth-Jones 1997)

The most serious side effects of cyclosporin are nephrotoxicity and hypertension. Both are dose dependent and of gradual onset. Cyclosporin can give rise to hyperuricaemia by reducing renal clearance of uric acid. It is also associated with neurological side effects including, dysaesthesiae, tremors and headaches. In spite of its immunosuppressive activity, its use in dermatology does not appear to cause internal malignancies or increased susceptibility to infection. It is recommended that hypertension should be treated, using agents, such as nifedipine or isradipine, that do not interact with CSA (to alter blood levels). (Koo 1997) Renal function should be monitored using serum creatinine. If this rises above 130% of the baseline value then CSA dosage should be reduced. It is of interest that in 1998 the FDA recommended that the upper dosage limit should be 4 mg/kg/day and that the creatinine threshold level should be 125% of baseline instead of 130%. (Koo 1997)

The contra-indications and monitoring recommendations are summarised in Table 2.5.

2.2.3.2 Methotrexate

Methotrexate has immunosuppressive and cytotoxic effects. It has been used in the treatment of psoriasis since the 1960s. It is thought to exert its effects in psoriasis through its immuno-modulatory effects. (Said 1997) It is recommended for short-term treatment, to gain control of unstable (pustular or erythrodermic) psoriasis and for long-term maintenance treatment. It is also indicated for patients with extensive chronic plaque psoriasis whose disease is inadequately controlled by topical therapy alone. (Chalmers 1997)

Methotrexate is well-absorbed from the gastro-intestinal tract (in doses of less than 25 mg) (Said 1997) and is usually given orally. The majority of the dose (60-90%) is eliminated via the kidneys, with biliary elimination accounting for less than 10%.

A single weekly dose is recommended, starting with dose of 5 - 7.5 mg and increasing in 2.5 mg increments according to clinical response and toxicity. A test dose of 5 mg should always be given, followed by a full blood count 7 days afterwards to identify patients who are exceptionally sensitive to the effects of bone marrow suppression. Few patients are expected to need more than 20 mg/wk to control their disease. Once satisfactory control has been achieved, the dose is adjusted to the

lowest dose needed to maintain control and the patient is monitored for adverse effects. Table 2.5 summarises the contra-indications to treatment with methotrexate and monitoring requirements.

The most common side effect is nausea, which characteristically appears within 12 hours of taking the weekly dose, and may persist for up to 3 days. It is usually mild but can be severe enough to warrant treatment. Folic acid has been found to be more helpful then conventional anti-emetics. Folic acid (5 mg) is given either daily or in a once-weekly course of three doses around the methotrexate dose.

Toxic effects on the bone marrow and liver are potentially serious. Acute myelosuppression requires immediate treatment with folinic acid. A rise in mean corpuscular volume (MCV) is commonly seen with long-term methotrexate therapy and is thought to reflect a relative folate deficiency. If the MCV does not return to normal with folate treatment then methotrexate should be discontinued. Hepatotoxicity is conventionally monitored using aminotransferase levels, which are unreliable indicators of hepatic fibrosis. Amino-terminal pro-collagen III provides a more accurate index of liver damage, and avoids the need for a liver biopsy, but is not yet in common use. (Chalmers 1997)

2.2.3.3 Etretinate and acitretin

Etretinate and acitretin are synthetic derivatives of vitamin A. They are thought to exert their effects in psoriasis through a variety of effects at cellular level, including effects on proliferation, keratinization and differentiation of epithelial cells and anti-inflammatory and immunomodulatory effects.
Etretinate was introduced first but was superseded within a few years by acitretin, which is its free acid metabolite. The two drugs have similar efficacy but acitretin was thought to have a better side-effect profile. Etretinate is strongly lipophilic and is sequestered in body fat where it has been detected as long as two years after discontinuation. Typically it has a half-life of up to 120 days whereas acitretin and the 13-cis-acitretin isomer have half-lives of 50 and 75 hours respectively. (Brindley 1989) Acitretin is negatively charged at physiological pH and is fifty times more hydrophilic than etretinate. (Wiegand 1998)

Oral acitretin has a bioavailability of approximately 60%, in the presence of food. (Brindley 1989) It is reversibly isomerized to 13-cis-acitretin *in vivo* and is eliminated in urine and in bile.
Further experience with acitretin has shown that some of the drug is re-esterified in vivo and so the advantages may be fewer than originally anticipated. (Almond-Roesler 1996)

Acitretin is indicated in patients with severe, extensive chronic plaque psoriasis whose disease has failed to respond to other treatments. It is also indicated for localised or generalised pustular psoriasis and for erythrodermic psoriasis.

Treatment should be started with a dose of 25-30 mg and increased after 2-4 weeks up to 50mg (or 75mg) according to response, for a further 6-8 weeks. (BNF 1998) Chronic plaque psoriasis responds slowly and the best effect is expected 2-3 months after the start of treatment. After clearing of the disease a maintenance dose of 0.2-0.4mg/kg/day is recommended for 3-6 months. (Gollnick 1997) Adjuvant topical treatment or phototherapy is recommended throughout the period of acitretin treatment. Suitable agents include, tar, dithranol, vitamin D3 analogues, UVB or PUVA treatment. Experts recommend that the combination of acitretin with other systemic agents, such as methotrexate, cyclosporin or fumarates, should be avoided because of the dangers of additive toxicity. (Gollnick 1997)

A large number of common side effects is associated with the use of acitretin. Mucocutaneous effects, such as drying and cracking of the lips, are seen frequently. Dryness of the nasal, buccal and conjunctival mucosae and peeling of the skin on the palms and soles are moderately common effects. An increased rate of loss of scalp hair is occasionally sufficiently severe to be noticeable. Other common complaints include skin "stickiness", skin fragility, nail fragility and itchiness.

Acitretin use is associated with a number of potentially serious side effects. There is a high risk of teratogenicity if acitretin is administered in the first three months of pregnancy and malformations of craniofacial, thymic, cardiac, skeletal and central nervous systems have been reported. Because of the persistence of the drug in body tissues, it is recommended that pregnancy be avoided for 2 years after the end of treatment.
Elevations of plasma lipid levels (increased LDL, decreased HDL) are relatively common as are elevations of liver enzymes.
Bone toxicity, including ossification of ligaments and tendons, bony spurs and diffuse hyperostosis, is common in patients receiving long term (1-3 years) treatment. Premature epiphyseal fusion has occurred and for this reason it is not recommended for use in children.

Table 2.5: Contra-indications and monitoring of systemic agents for treatment of psoriasis

(after Gawkrodger 1997)

2.2.3.4 Other systemic treatments including alternative and unlicensed treatments.

Azathioprine and hydroxyurea have been used for psoriasis but tend to be less effective than methotrexate and more likely to cause myelotoxicity. (Hunter 1995) Sulphasalazine has been found to be helpful in small number of patients. (Gupta 1990) Fumarates (a mixture of fumaric acid and its esters) are used in the Netherlands and in Germany but there is no licensed preparation in the UK. Newer immunosuppressive agents such as tacrolimus and mycophenylate mofetil are under investigation. Future treatments are likely to involve agents which modify T-lymphocyte or cytokine functions (Clark 1999)

2.3 Conclusions

Psoriasis affects a large number of people and accounts for substantial morbidity. The ideal treatment would be efficacious, present few risks, be convenient to use and be inexpensive. The available treatments combine these attributes in varying proportions, but none is ideal. The selection of a treatment depends on the site and severity of disease and the patient's preferences. Patients with severe psoriasis require careful monitoring because the disease is dynamic and may require periodic modifications to treatment. Furthermore, several of the available treatments are associated with cumulative toxicity. Regular monitoring and review of treatment therefore provides the opportunity to maximise the benefit/risk ratio for the individual patient.

Chapter 3

Outcome measures in psoriasis treatment

Summary

Outcome measures are required to assess efficacy in trials and to monitor the responses to treatment. Outcome measures for psoriasis can be measures of the physical effects, measures of the impact of the disease or composite measures. Investigators or doctors administer the majority of outcome measures but the self-administered PASI has been developed for use by patients.

Standardised, valid, reliable outcome measures are important in the assessment of any drug treatment. Ideally, outcome measures should also allow comparison of drug treatment with other forms of treatment. Thus, in psoriasis, the ideal outcome measure would allow comparison between topical treatment, systemic treatment and phototherapy.

The outcome measures that have been used in psoriasis can be broken down into two categories, namely, measures of the physical effects of the disease and measures of the impact of the disease. (see Table 3.1)

Table 3.1: Outcome measures for psoriasis treatment

Category	Outcome measure	Scale/Units
Measures of the physical effects of psoriasis	Trans-epidermal water loss (TEWL)	G/m^2/hour
	Chromameter readings	Erythema "a" scale
	Cutaneous blood flow (measured by laser velocimetry)	Laser-Doppler velocimetric reading
	Erythema	5 & 7 point scales
	Induration	5 & 7 point scales
	Desquamation	5 & 7 point scales
	Surface area affected	%
	Psoriasis Area and Severity Index (PASI)	0-72
	Self-administered PASI (SAPASI)	0-72
	Clearing	%
	Overall skin condition	Subjective description
Measures of the impact of psoriasis	Handicap	) Numerical value) depending on) instrument
	Social disability	
	Quality of life	
	Impact on life (patient's assessment)	Visual analogue scale
	Days of hospitalisation	Days
	Days of remission	Days
Composite measures	Salford Psoriasis Index	x:x:x (3 figure score)
	Dermatology Index of Disease Severity (DIDS)	5 point scale

3.1 Measures of the physical effects of psoriasis

Measures of the physical effects of psoriasis range from objective, instrumental measures such as trans-epidermal water loss and cutaneous blood flow measurements using laser-Doppler velocimetry to subjective assessments such as the extent of disease clearing.

Objective measures have been sought for each of the prominent features of psoriasis, namely the erythema, induration (thickening) and scaling of the psoriatic plaques. In some trials attempts have also been made to correlate instrumental measurements with clinical gradings. In one study a two-week bilateral comparison of betamethasone valerate against white soft paraffin, the subjective scores assigned by a single observer (erythema, plaque elevation, scaling and a composite score) were similar to objective measures (computer image analysis, erythema reflectance, nitric oxide production, ultrasound scan for thickness, scale and echo-poor zone. (Ormerod 1997) Other studies have also demonstrated that visual assessments of skin erythema correspond with measurements obtained by a laser Doppler flowmeter, a spectroradiometer and erythema meter and a chromameter. (Serup 1990; Lahti 1993) Measures of scaling are less well-developed, and although optical profilometry and scanning macro-photographic densitometry methods have been used, the clinical relevance of the results is not yet clear. (Marks 1996) Plaque thickness has been measured using mechanical callipers and ultrasound. (Lawrence 1986) Exudation of tissue fluid during the use of the callipers has been a problem and the ultrasound method has been recommended as the more accurate of the two.

A further practical drawback of the laboratory type of measurements is that they can only be applied to small areas, whereas the disease often affects several areas of the body and there may be considerable differences between the plaques in different areas. Instrumental measurements may therefore be more suitable for monitoring drug effects on two comparable lesions than for overall monitoring of disease progress.

It has been suggested that plaque thickness is the most reliable of the clinical signs of psoriasis. (FDA Advisory Committee (1998)). The main reason for this is that erythema is affected by factors such as blood flow and ambient temperature and may be exacerbated by some treatments. Scaling can be reduced considerably by treatment with keratolytics and emollients.

Many trialists have chosen to monitor outcomes in psoriasis by estimating clinically the extent of erythema, induration and desquamation, the three main features of the condition. These have been assessed in a quasi-objective fashion using five or seven point scales. The proportion of the body surface affected by the disease has also been used as an outcome measure.

In 1978 a composite measure, the Psoriasis Area and Severity Index (PASI), was devised to take account of both the extent and severity of the disease (Fredriksson 1978). The formula for the PASI can be written as:

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

Where E= erythema, I =infiltration (thickening) and D = desquamation, each assessed on a scale of 0-4; A= area affected by psoriasis: 0 = none, 1 = 10%, 2 = 10-29%, 3 = 30-49%, 4 = 50-69%, 5 = 70-89% and 6 = 90-100%.; h = head, t = trunk, u = upper limbs and l = lower limbs.

The PASI is widely, although not invariably, used in clinical trials, however it remains unvalidated. It is also used routinely in specialist psoriasis clinics. Its appeal is that it relies on clinical assessments that can be made easily by an experienced practitioner, without need for additional equipment. The main disadvantages are the relative insensitivity to some changes in the pattern of disease and the risk of inter-assessor variation. For example, mild, extensive disease could achieve the same PASI score as severe disease affecting a small area. In the clinical context this could mean that a case of psoriatic erythroderma, with widespread, moderate erythema, induration and scaling could have an identical score to a case of chronic plaque psoriasis involving 10-30% of the body surface area (van der Kerkhof 1992). Whereas the second case is relatively easy to treat, the first is severe and almost invariably requires hospital admission.

In 1998 Finlay (Finlay 1998) drew attention to the fact that an error in the original description of the PASI may have given rise to some inconsistencies in its use. In the original description, 30% of the body surface areas was assigned to the trunk and 20% to the upper limbs, but these proportions were transposed in a later paragraph. The test error has been repeated but it is not known to what extent, if at all, the incorrect formula has been used.

3.1.1 Body surface area estimation

Given the patchy distribution of much psoriasis, the assessment of the amount of skin involved is not always straightforward. As this is a major component of the PASI, a number of methods have been devised to improve the accuracy and reproducibility of this measurement.

Ramsay and Lawrence (Ramsay 1991) compared three methods, clinical estimation, image analysis of traced plaque outlines and image analysis of whole body photographs.
The rule of nines, which was originally devised to estimate the surface area of burns, was used to estimate body surface area. It assumes that the total body surface comprises 9% for the head and neck, each arm, the front and back of each leg and the four trunk quadrants, leaving 1% for the genitalia. Using this as a guide, the clinician then estimates the proportion of each area affected by

the disease and calculates the grand total. In the study, four untrained observers estimated the average extent of psoriasis to be 14-33% of body surface area. Measuring the areas of tracings of plaque outlines by computerised image analysis gave a mean value of 9% while image analysis of whole body photographs gave a mean value of 7%. The authors concluded that untrained observers using the 'rule of nines' would always overestimate the extent of the disease.

Another popular clinical measure uses the flat, closed hand. The area that it can cover has been assumed to be 1% of body surface area, and in some cases this offers an easier way to estimate the total area affected by psoriasis. (Stern 1986) Planimetric measurements now suggest that a hand area actually represents 0.070 –0.076% of the BSA, (Long 1992) and therefore the hand measure could be expected to overestimate the BSA affected.

Bahmer explored the use of grid point counting to improve the accuracy of body surface area estimation. (Bahmer 1989) This involved laying a grid over photographs of psoriatic plaques and counting the number of intersections over each plaque. The main drawback of this technique is the time involved. It seems likely that future methods for estimating the extent of disease are more likely to rely on developments in the field of computerised image analysis. Early instruments were unable to handle curved surfaces but this technical problem may be solved in future.

3.1.2 Assessment by patients

Investigators or doctors administer all of the measures described so far. In 1994 Fleischer devised the 'self-administered PASI' (SAPASI) as a means of enabling patients to estimate the physical effects of their own disease. (Fleischer 1994) The general formula for the Patient PASI (later called the self-administered PASI) is:

$$SAPASI = (0.1A_H + 0.2A_U + 0.3\ A_T + 0.4\ A_L)\ (4 \times (VAS_E + VAS_I + VAS_S))$$

Where A_H = head area score, A_U = upper extremity area score, A_T = trunk area score, A_L = lower extremities score, VAS_E = VAS erythema score, VAS_I = VAS induration score, VAS_S = VAS scale score. Area scores were assigned a numeric value of 1- 6, corresponding to 0% to 100% body surface area affected. These were derived from line drawing silhouettes on which the patients shaded the areas affected. An investigator who had not evaluated the patients then estimated the proportion of the total area affected and assigned the numerical value. For the VAS scores, patients were asked to score an average psoriatic lesion for erythema, induration and scaling on separate, 120-mm VAS scales. Each of these was labelled with descriptions, for example, the induration scale had the descriptions: no thickness, feels firm, raised, thick and very thick. VAS scores were

recorded in millimetres. Like the conventional PASI, the SAPASI returns a maximum possible score of 72.

A later study showed that the method had good test-retest reliability ($r = 0.82$, $p=0.0001$) and that the results correlated well with PASI scores assigned by physicians (Feldman 1996). They also reported that the SAPASI varied in parallel with the PASI as patients' clinical status changed. Given that the SAPASI was administered by untrained individuals, these findings suggest that it could be a useful measure for estimating disease severity and responses to treatment when trained personnel were not available, for example, for remote monitoring of disease progress.

3.2 Measures of the impact of psoriasis

Dermatologists' assessments of psoriasis have tended to focus firmly on the physical effects of the disease whereas patients have a different viewpoint and, when asked to assess disease severity take into account other factors. In one study 21 dermatologists and 56 patients were asked to rank a list of 50 features considered to be characteristic of psoriasis. (Baughman 1970) Patients rated 'embarrassment over appearance' as most characteristic of severity, while dermatologists considered this to be the least important. This is one of the factors that have prompted growing interest in quality of life (QOL) measures in psoriasis. (McKenna 1996)

QOL measures may be generic, disease-specific or specialty-specific. Generic instruments are designed to assess a complete spectrum of dimensions applicable to a variety of health states or diseases. They have the advantage that they allow comparisons of the impact of different diseases and may uncover non-specific effects of a disease or its treatment. The disadvantage of generic measures is that they may not include elements specific to skin diseases and may therefore be insensitive to changes in the severity of psoriasis.

A number of specific QOL instruments have been developed for use in psoriasis (see Table 3.2). These instruments differ considerably in the ways in which they have been constructed and in the domains covered. Two of the instruments, the Psoriasis Disability Index (PDI) and the Psoriasis Life Stress Inventory (PLSI have been compared with PASI. In the case of the PDI, the correlation coefficient (r_s) was 0.40 ($p<0.05$, $n=32$), indicating a modest correlation between the two measures. (Finlay 1990) However, in a larger study, a comparison of the PLSI and the PASI in 132 psoriasis outpatients found that the PLSI scores were independent of clinical severity assessed by PASI. (Fortune 1997)

Ashcroft and colleagues conducted a critical appraisal of the available QOL measures for psoriasis. (Ashcroft 1998) The authors noted that interpretation of QOL scores and changes in the scores over time had to be approached with caution. Improvements in QOL scores may reflect psychological adaptation to the condition rather than actual changes in health or symptoms.

Table 3.2 : QOL measures for patients with psoriasis

Instrument	Source	Features
Psoriasis Disability Index (PDI)	Developed after questioning 54 psoriasis patients	15 questions covering 5 domains (daily activities, work or school, personal relationships, leisure and treatment) Based on previous month
Psoriasis Life Stress Inventory (PLSI)	Originally based on experience with 50 patients; modified with responses from 217 further patients.	15 questions (cosmetic disfigurement, social stigma, coping with physical aspects of disease, treatment) Based on previous month
Dermatology Life Quality Index (DLQI)	Responses from 120 outpatients with a range of skin complaints.	10 questions to assess disability Based on previous 7 days
Children's Dermatology Life Quality Index (CDLQI)	Responses from 169 children with a range of skin complaints.	10 questions to assess disability in children Based on previous 7 days
Dermatology Quality of Life Scales (DQOLS)	Derived from responses from 50 dermatology outpatients.	41 questions covering 3 domains (psychosocial aspects, physical activities, symptom scales) Designed to complement the DLQI
Skindex	Based on a literature view and responses from clinicians and patients.	61-question and 29-question versions

3.3 Composite measures

Many published studies have included 'global scores' for psoriasis. Whilst at first sight these are highly subjective and therefore likely to show wide inter-assessor variation, it could be argued that they represent dermatologists' legitimate attempts to capture the severity, extent and impact of the disease in one figure. Recently, two composite measures have been developed in order to tackle the shortcomings of the PASI and, effectively, to codify the global assessments. These are the Salford Psoriasis Index (SPI) and the Dermatology Index of Disease Severity (DIDS).

The DIDS was developed for staging inflammatory skin diseases and uses the percentage body surface area affected and functional limitations to score on a five-point scale. (Faust 1997) Concerns have been expressed that the DIDS may not be sufficiently sensitive to track changes during treatment and that it fails to take account of psychological morbidity, which does not always correlate with the extent of disease. (Williams 1997)

The Salford Psoriasis Index (SPI) was developed to match the clinical decision-making process by providing an assessment of three main factors taken into account when planning treatment for a patient with psoriasis. (Kirby 2000) These are clinical signs, psychosocial disability and previous treatment. The index takes the form of three figures and is analogous to the tunour:nodes:metastasis (TNM) grading that is used for cancer staging. In this case the first figure is derived from the PASI score, using a scale that converts it into a point on a 0-10 scale. PASI values above 37 score 10, and this in keeping with the observation that scores above 37 are rarely seen in practice and so the upper end of the PASI scale is practically redundant. The second figure indicates the psychosocial impact of the disease, and is assessed by the patient using a visual analogue scale graduated from 0-10. The third figure reflects the historical severity of the disease as shown by the number of episodes of erythroderma, the number of admission to hospital and the need for systemic treatment (including PUVA). Each systemic treatment, including PUVA, is given a score of 1 if given for less than 12 months or 2 if given for longer. One extra point is added (i) for every five admissions for inpatient treatment, (ii) if the total cumulative dose of PUVA exceeds 200 treatments or 1000 J/cm^2, and (iii) for each episode of erythroderma. The individual components of the SPI have been validated by comparison with known measures of disease severity. When tested on a cohort of 20 patients before and after a period of six weeks' treatment, the first two figures decreased significantly, but as expected, the third figure, which reflects historical severity, did not change.

3.4 Conclusions

The availability of a suitable outcome measure is essential for the assessment of response to treatment. In practice, outcome measures are required for two main reasons, first to measure efficacy in clinical trials and second to monitor the response to treatment in day-to-day practice. It can be argued that the former requires a dichotomous endpoint (clearing vs. no clearing or clear/almost clear vs. no clearing) but the latter requires a measure that is sensitive to progressive changes. The PASI has been widely, but not universally, used in both situations. In clinical trials, some authors have used the PASI score to show their results both as continuous variables and as a dichotomous variable, using a 75% decrease in the PASI as the cut-off point. This seems to be analogous to 'almost clear'. Others have preferred the 'physician's global assessment'. Randomised, controlled trials published to date have mainly used one of these two outcome

measures. It may be that, in future, the SPI may offer a transparent, systematic way of deriving a global assessment.

Chapter 4

Previous analyses of psoriasis treatment

Summary

Nine reports of economic analyses of psoriasis treatment have been published and one systematic review. (see Table 4.1) None has so far provided a comprehensive basis for decision-making or for the formulation of prescribing guidelines in the UK. Nevertheless, these studies have served to identify some of the problems associated with systematic reviews and economic analyses of psoriasis treatment.

4.1 Introduction

Analyses of treatment may take the form of systematic reviews, with or without meta-analyses and economic analyses. They may also take the form of economic analyses based on theoretical (decision-analytic) models. The main purpose of any of these analyses is to synthesise the available information in such a way as to provide robust estimates of effect sizes and costs. It follows that any analysis of treatment must make explicit its sources of data, analytical methods and the assumptions that have been made in performing the analysis.

Systematic reviews are primarily focused on the effectiveness of treatments, whereas economic analyses are focused on costs and consequences of treatment (as described in Chapter 1). Both can be used to inform decisions about treatment for individuals and for populations, and are essential if an evidence-based approach is required.

Table 4.1: Analyses of psoriasis treatment

Author/year country	Study type	Treatments included	Methods
Chen 98 USA	CEA (CUA) & CBA	Methotrexate vs. Goeckerman therapy	Utility values determined by VAS and WTP
Cork 93 UK	Cost analysis	Impact of introduction of calcipotriol on treatment costs	Costs of treatment.
Davies 97 UK	CEA	Cyclosporin dithranol & UVB	Decision analytic modelling; summary estimates of success rates and relapse rates drawn forma small number of trials.
Einarson 94 Canada	CMA (CEA)	Cyclosporin, methotrexate, retinoids, PUVA	Meta-analysis to derive summary estimates of clinical success, relapse rates and side effects + decision analytic modelling.
Ellis 87 USA	CEA (?)	Etretinate vs inpatient treatment	Estimates of treatment costs and episodes of hospitalisation before, during and after etretinate treatment.
Feldman 97 USA	Cost analysis	All (not specified)	Postal survey; patient-reported costs and SAPASI
Krueger 84	Cost estimates	All (not specified)	No details given.
Sander 93 USA	Cost analysis	Phototherapy (Goeckerman, PUVA and outpatient UVB) and oral therapy including hydroxyurea	Costs of treatment for ten patients receiving each of seven types of treatment.
Snellman 98 Finland	Cost analysis	Heliotherapy	Follow up of 46 patients. Direct and indirect costs estimated.
Spuls 97 The Netherlands	Systematic review	Systemic treatments (including UVB)	One third of trials included were not RCTs. Analytical methods not clearly described.

4.2 Economic analyses

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.

4.2.1. Economic analyses of psoriasis treatment conducted in the UK

Cork 1993

Cork (Cork 1993) 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 in-patient admissions was reduced by 50% (for one consultant). There was also 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 PUVA. According to the author these observations suggested that calcipotriol use obviated the need for second line therapies such UVB and methotrexate. However, it is also possible that this change in prescribing patterns was a "new drug phenomenon", that is the characteristic surge in prescribing of a new product. This could have been confirmed or refuted had there been a rigorous evaluation of the patient outcomes as well as the input costs.

Davies 1997

Davies and colleagues (Davies 1997) 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 one year with short course cyclosporin at 5mg/kg/day was £1473 whereas the corresponding daycare treatment cost was £2815.

4.2.2. Economic analyses of psoriasis treatment conducted outside the UK

Krueger 1984

Krueger and colleagues (Krueger 1984) reported estimated costs for out-patient and in-patient treatment of psoriasis but gave no details of the methods used to gather the data. Patients with psoriasis were reported to spend $650 per year on medication costs, laboratory tests and physician fees. Inpatient treatment was estimated to cost $10,000 per year (on the basis that each hospital stay lasted 21 days at a cost of $500 per day).

Feldman 1997

Feldman and colleagues (Feldman 1997) 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 time spent on psoriasis care, total charges/expenses, out-of-pocket expense for psoriasis care, number of prescriptions and OTC medicines. Psoriasis severity was assessed using the Self-administered PASI (SAPASI) which had been previously validated. No results are presented to show the types of therapy that the patients were receiving.

The SAPASI 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 increase with disease severity.

The estimated total annual expense in caring for psoriasis was $800 per patient, which was similar to Krueger's 1984 estimate of $650 (Krueger 1984). However, the authors point 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 which they used however, no data on comparative treatment costs are presented.

Sander 1993

Sander and colleagues (Sander 1993) 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 (except for cyclosporin where six were used) who had received it as monotherapy were selected and their records were used to identify costs. 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 + range). Mean costs ranged from $1131 (hydroxyurea) to $6648 (cyclosporin). The authors concluded that their data would help practitioners and health care 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 this study a small number of records was used and it is questionable whether the data would be representative for the authors' institution . For example, there was a five fold variation in the annual costs for out-patient UVB treatment. This level of variance makes it unlikely that the results could be generalised to a wider population. Although the authors presented a table of clinical response rates these data were not used in the interpretation of the cost data. The final cost analysis compared all regimens as though they were equally effective. Had the differing outcomes been taken into account, a different picture may have emerged.

Ellis 1987

Ellis and colleagues (Ellis 1987) investigated the impact of etretinate therapy on inpatient treatment costs in a group of 26 patients with histories of hospitalisation for psoriasis. During the

etretinate treatment period patients were hospitalised for 0.2 ± 0.1 days per year compared with 13.8 ± 2.4 days per year in the pre-etretinate treatment (control) period. The authors estimated the corresponding treatment costs to be $2,300 per year (on etretinate) and $10,000 (control, pre-etretinate) per year. The calculations for the costs of inpatient treatment (pre-etretinate) did not take account of additional outpatient expenses, lost working days or intangible costs.

Snellman 1998

In 1998 a Finnish study examined the effect of heliotherapy on the costs of psoriasis. (Snellman 1998) The costs of psoriasis treatment in 46 patients were monitored for one year before, during and for one 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 in-patient treatment. As the heliotherapy was delivered in the Canary Islands and all other costs related to the Finnish health care system, it would clearly be impossible to generalise Snellman's results to other populations.

Einarson 1994

In 1994 Einarson and colleagues (Einarson 1994) 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 5mg/kg/day for a period of 6 weeks. They also pointed out that, because of the reimbursement paid by the province, their results might not be generalisable to other provinces or countries. Two other criticisms may be levelled at this study. First, some details of the methods used to calculate cost avoidance were not explicit. Second, the trials used for the meta-analysis of etretinate therapy concerned mainly palmo-plantar pustular psoriasis, which is believed to respond better to retinoid treatment than does chronic plaque psoriasis. Furthermore, the methotrexate data were based on a single study. As this analysis assumed that the outcomes from all treatments were the same it is probably best described as a cost-minimisation analysis.

Chen 1998

Chen and colleagues (Chen 1998) reported a cost-effectiveness and cost-benefit analysis of using methotrexate vs. 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 CEA were

highly sensitive to the utilities used, which were generated from three groups, patients, healthy non-experts and dermatologists. The CEA showed that for all three groups, Goeckermann therapy should be chosen in preference to liquid methotrexate for severe psoriasis. This contrasted with the CBA, which suggested that liquid methotrexate rather than Goeckermann therapy should be provided for psoriasis of all grades of severity. This clearly illustrates the point that an analysis based on patient preferences may have very different results from an analysis of same situation based on costs alone.

Although the authors described this as a CEA, the method appears to describe a cost-utility analysis. The decision-analytic model includes both the possible outcomes and corresponding utilities. The authors say that the "effectiveness" calculation is described in the methods section but it appears to be absent and so it is not clear how the terms described as cost-effectiveness ratios were derived. It is confusing that the results of the analysis are expressed in a dollar value alone and not, for example, dollars per Quality Adjusted Life Year. The authors say, "to be considered effective, the CE ratio cannot exceed the traditional threshold of $35,000. This threshold is derived historically from the CE ratio of haemodialysis compared with no dialysis for chronic renal failure" However, this figure is usually quoted as the cost per QALY.

The CBA in this study was based on the differences between the costs of providing treatment and the monetary value of the benefits determined by willingness to pay.

4.3 Systematic review of psoriasis treatment

The only previously published systematic review of treatments for severe psoriasis was carried out by Spuls and colleagues in The Netherlands. (Spuls 1997) In this study the authors systematically reviewed the evidence concerning the ability of five systemic treatments to induce remission in patients with severe psoriasis. They analysed 129 patient series, reporting on 13,677 patients. They concluded that PUVA therapy was associated with the highest proportion of patients with clearance (70%) followed by UVB (68%) and cyclosporin (64%). They also noted that side effects were most frequent in patients treated with retinoids and least frequent in the phototherapy group.

Unfortunately the methods that this group used were not described explicitly. It is of particular concern that only one third of the trials included in the analysis were randomised-controlled trials. The authors commented that their review could not focus on an estimate of the treatment effect based on comparisons of outcomes in parallel groups randomly allocated to the treatments under study, because of the "absence of suitable comparative clinical trials". Instead, they focused on treatment outcomes in patient series. (Thus, for example, a study comparing cyclosporin with PUVA would generate two patient series) For each series, the proportions of patients achieving complete clearance (95-100% clearance), good (more than 75% clearance), moderate (50-75% clearance) and poor (less than 50% clearance) responses were extracted. In each case the outcome

measures used by the original trial authors were used. These included PASI, body surface area affected and average global scores. The results were pooled using size-weighted averages. These were then presented as measures of effectiveness. The study also reported the frequency of side effects and drop-outs due to side effects, however the authors noted that a number of the trials included in the review did not report these items.

Spuls and colleagues acknowledged that the inclusion of non-randomised trials could have led to some problems. They suggested that there may have been selection biases in the original studies, resulting in, for example, patients with more severe disease being recruited to cyclosporin trials than for PUVA trials. Another issue was the use of different trial endpoints; phototherapy trials are invariably based on disease clearance (full remission) whereas the induction of remission is usually the endpoint for trials of other systemic therapies. Other issues identified included the use of different outcome measures and variable reporting of drop-outs and side effects. These considerations mean that the response rates reported in this study cannot immediately form the basis for further analyses.

4.4 Conclusions

What is required is a systematic review of randomised, controlled trials of treatments for severe psoriasis that could provide meaningful estimates of effect sizes, with confidence intervals. This type of information would be helpful to clinicians in formulating treatment strategies and to patients in determining the balance of risks and benefits associated with each type of treatment. In addition, as a first step, cost-effectiveness analyses of the main systemic treatments, in the context of the UK healthcare system, are needed. These would form useful benchmarks against which future treatments could be evaluated and could lay the foundations for future cost-utility analyses.

Chapter 5

Decision-analytic model for treatment of moderate-severe, chronic plaque psoriasis

Summary

A decision-analytic model is central to any decision analysis. Such models must follow a set of accepted conventions. A model has been proposed for analysis of the treatment of moderate-severe, chronic plaque psoriasis. The assumptions that underpin the model are explored and the strengths and weaknesses of the approach evaluated.

5.1 Decision-analytic models

Decision analysis is a systematic, quantitative technique for structuring the decision-making process. Each analysis hinges on the construction of a decision analytic model that structures the problem in such a way as to show the decisions and outcomes, in a time sequence. For convenience this is often depicted as a 'decision tree'. The tree must distinguish between choices (which are under the decision-maker's control) and chance events (which are beyond the decision-maker's control). These are represented by 'nodes' in the model. Two basic rules must be obeyed when constructing the tree; firstly, the branches from a node must be exhaustive and mutually exclusive and, secondly, the sum of probabilities in each branch must be equal to one. This process has been described in detail in Chapter 1.

5.2 Decision-analytic model for treatment of severe psoriasis

Einarson and colleagues, in Canada, (Einarson 1994) proposed a decision analytic model for the treatment of severe psoriasis. (Figure 5.1). This was constructed using information from current treatment guidelines and meta-analysis of published trials and was validated by a panel of dermatologists. The treatments compared were cyclosporin, methotrexate, etretinate and PUVA. The model was applicable to each of the four treatments and assumed that if the primary treatment failed, a secondary (back-up) treatment would be used. If cyclosporin was the primary treatment then methotrexate was the secondary treatment. Cyclosporin was the secondary treatment for methotrexate, etretinate and PUVA.

The decision analytic model can be written in spreadsheet form (as explained in Chapter 1). In the model there are four stages at which there are chance nodes with associated probabilities. These are shown in table 5.1 as Probability 1, Probability 2 etc. The overall probability of an outcome is calculated by multiplying the probabilities in the row together and then adding together the results for all the rows with the same outcome. In this case, rows 1,2,3,5 and 6 should be added for the overall probability of treatment success, using a specified combination of primary and secondary treatments.

Table 5.1: Einarson's model – general scheme in spreadsheet format

No	Description	prob factor 1	prob factor 2	prob factor 3	prob factor 4	Outcome
1	Total success	PSR	1-PRR	1	1	success
2	success,relapse,success	PSR	PRR	PRSR	1	success
3	success,relapse,failure,success	PSR	PRR	1-PRSR	SSR	success
4	success,relapse,failure,failure	PSR	PRR	1-PRSR	1-SSR	re-evaluate
5	failure,success	1-PSR	SSR	1-SRR	1	success
6	failure,success,relapse,success	1-PSR	SSR	SRR	SSR	success
7	failure,success,relapse,failure	1-PSR	SSR	SRR	1-SSR	re-evaluate
8	Total failure	1-PSR	1-SSR	1	1	re-evaluate

PSR Primary treatment success rate
PRR Primary treatment relapse rate
SSR Secondary treatment success rate
PRSR Primary retreatment success rate
SRR Secondary treatment relapse rate

Many of the assumptions made by the Canadian group were not made explicit in the report and close examination of the model suggests a number of issues that need to be taken into account if it is to be used for future analyses.

5.2.1 Duration of treatment

It is not clear from the report whether the model assumes that treatments are given continuously or intermittently. Although, at first glance it, appears that intermittent treatment was envisaged, the fact that the relapse rates quoted were derived mainly from groups of patients receiving maintenance treatment (with one of the four agents in the comparison) suggests that continuous treatment was, in fact, expected. This presents some problems in the light of current knowledge.

For example, it would no longer be acceptable to offer continuous treatment with either PUVA or cyclosporin.

5.2.2 Estimation of success rates

It is logical to use the pooled results of RCTs to estimate the success rate as RCTs provide the most stringent test conditions for a treatment. In this study no details were given about the search strategy for trials concerning the four treatments involved in the analysis and, therefore, it was not clear which types of trial were eligible for inclusion. Furthermore, there was no indication of how 'success' had been defined. This is also important, as has been argued earlier. As different definitions of success clearly influence the eventual success rate.

The trials used for the meta-analysis of etretinate therapy concerned mainly palmo-plantar pustular psoriasis, which is believed to respond better to retinoid treatment than does chronic plaque psoriasis. This almost certainly over-estimated the probable success rate in the more common, chronic plaque psoriasis, which was the subject of the analysis.

Cyclosporin response rates were derived from four trials. Three were RCTs comparing cyclosporin with placebo (Ellis 1991, Guenther 1991 and van Joost 1986) and one was a non-randomised comparison of cyclosporin and PUVA. (Petzelbauer 1990). Curiously, the other placebo-controlled RCT that had been published in the same period (Engst 1989) was not included.

Methotrexate response rates were based on a single study that focused primarily on the treatment of psoriatic arthritis. (Willkens 1984)

5.2.3 Estimation of relapse rates

Relapse rates were appropriately derived from a mixture of randomised trials and long-term open trials. The main difficulty here was the lack of clarity about the definition of 'relapse'. In attempting to reproduce the figures cited in Einarson's study it became clear that the relapse rates quoted were derived mainly from groups of patients receiving maintenance treatment (with one of the four agents in the comparison) (See 5.2.1). Two examples serve to illustrate this point: First, the report cites a relapse rate of 62% (811/1308) derived from the trial of PUVA therapy by Melski and colleagues (Melski 1977). There were 1308 patients in the trial; after induction of remission, they were divided into 4 groups, three of which received ongoing, low dose PUVA. Only one group

received no maintenance treatment and this is the group from which the relapse rate should be derived. As the reported relapse rate is based on the total number of patients in the trial, it must also include those receiving maintenance treatment. Second, they cite a trial of PUVA and UVB by Momtaz and Parrish (Momtaz 1984), from which a relapse rate of 31.3% (5/16) has been derived. This represents the relapse rate for the patients given maintenance PUVA, whereas in the five patients who had no active treatment there were three relapses in two months, that is a relapse rate of 60% in two months.

This is particularly confusing as Einarson's report says, "We did not incorporate maintenance therapy into the PUVA regimen as we could find no studies that fit the criteria of the meta-analysis and that assessed this question." While these figures might be appropriate if continuous treatment is envisaged, other estimates would be needed if intermittent treatment were planned, to reflect relapse rate after treatment is discontinued. The situation was further complicated by the fact that relapse rates appeared to relate to varying time periods.

5.2.4 Handling of side effects

The report refers to a meta-analysis for side effects and yet it is not clear how this was used in the final analysis.

5.2.5 Appropriateness of economic analysis

In the report by Einarson and colleagues, the analysis is described as both a cost-effectiveness analysis and a cost-minimisation analysis. Cost-effectiveness analyses express the results in terms of natural units, for example, cost per life saved or cost per episode of infection avoided. Cost-minimisation analyses compare only costs because, by definition, they assume that the outcomes of each of the treatment options are the same. The only situation in which these two types of analysis are interchangeable is when the outcomes of each of the treatment options are identical. If different treatments are associated with different success rates and different patterns of relapse then a cost-effectiveness analysis may be more meaningful. This could result in an analysis that compared the modelled strategies and expressed the results as cost per flare up avoided or cost per treatment failure avoided.

5.2.6 Application of the model

It is not clear from the report whether the model is intended to cover a one-year time period, although this is implied. The method says simply, "Because the analysis was extended for one year, therapeutic relapses were included." In addition the details of the sensitivity analyses are sketchy and insufficient to allow reproduction.

5.3 Discussion

It would have been reasonable to assume that the trials selected for the estimations of success rates would be RCTs, concerned with the treatment of chronic plaque psoriasis, using up-to-date doses or regimens, however, this is not the case in Einarson's study. The fact that at least one RCT that had been published within the same time frame as those used was missing suggests that the process for gathering the trials was not systematic. This could have influenced the estimate of pooled effect size. Furthermore, the very small standard errors cited would give rise to very narrow confidence intervals. These appear to have arisen due to the method used for pooling the data (which was Bayesian rather than one of the conventional approaches)

Overall the data collection appears to have been incomplete (in that at least one RCTs was missing), inconsistent (in that RCTs and other trials were admitted) and inappropriate (in that data were taken from trials concerned with palmo-plantar pustular psoriasis for application in chronic plaque psoriasis).

Given the number of inconsistencies and gaps in information it is difficult to feel confident about the results of Einarson's analysis. One element of the studies reported here was to populate Einarson's model with more robust data. Effectiveness data was obtained from a systematic review of the literature concerned with treatment of chronic plaque psoriasis and UK cost data were gathered.

5.4 Conclusions

Einarson's analysis should be repeated using values derived from the systematic reviews described in chapters 7-10 for effect sizes (success rates) and data derived from recent trials for relapse rates. Economic analyses should then be performed using current UK costs. All analyses should make clear whether continuous or intermittent treatment is under consideration. If trial data exist to show the pattern of relapse and re-treatment in real life then it may be possible to incorporate these into a revised model and compare the results.

Figure 5.1: The decision-analytic model proposed by Einarson and colleagues (Einarson 1994)

KEY: PSR – primary treatment success rate; PRR – primary treatment relapse rate; SSR – secondary treatment success rate; SRR – secondary treatment relapse rate; PRSR – primary retreatment success rate

Chapter 6

Meta-analyses of treatments for severe psoriasis

Summary

This chapter describes the methods of meta-analysis and the general approach used in this project for meta-analyses for psoriasis treatments.

6.1 Methods

6.1.1. Definition and description of meta-analysis

Meta-analysis is a technique for combining quantitatively the results of previous studies to derive summary conclusions about a body of research. It is particularly useful to summarise research where individual studies have been too small to yield conclusive results on their own. The results of meta-analyses are usually displayed as 'forest plots' in which the effect size from each trial is shown with its confidence interval. 'The line of no difference' (which corresponds to the value of unity for odds ratio and rate ratio but corresponds to zero for rate difference) is marked and the pooled effect size is shown. The advantage of this form of display is that it conveys a clear visual image of the results. For example, Collins and colleagues conducted a meta-analysis of randomised trials of diuretics for pre-eclampsia in pregnancy. (Collins 1985) They found nine trials; five showing a positive effect and four showing equivocal results. A meta-analysis of the data showed an overall positive result. (Figure 6.1)

Figure 6.1: Odds ratios for pre-eclampsia and 95% confidence limits in nine trials of diuretics. (Odds ratios less than unity represent beneficial effects of diuretics. Meta-analysis based on fixed effect assumption) (Collins 1985)

Meta analysis is often applied to randomised controlled trials (RCTs), however it is also possible to combine the results of case-control studies in this way. This is useful when there are many studies of low statistical power. As the treatments for psoriasis (both drugs and phototherapy) are amenable to RCTs, the remainder of the discussion will relate only this type of study.

6.1.2 Identification of studies for meta-analysis

The studies included in a meta-analysis must be closely similar in terms of patients and the intervention under investigation. Sackett and colleagues suggest that "Meta-analysis is on the strongest ground when the methods employed in the primary studies are sufficiently similar that any differences in their results are due to the play of chance." (Sackett 1991) If this is not the case, it may still be possible to combine the results statistically but the result may have little value in the clinical situation. It is important that the component studies are free from bias (or minimally biased) and therefore they should be randomised trials, ideally with intention-to-treat analysis, complete follow-up information, and objective or blinded outcome assessment. (Peto 1987)

The search for studies should be exhaustive and should follow the steps outlined in Chapter 1. Once eligible studies have been identified they are retrieved and checked. This is an important step as it is not always possible to tell from the title and abstract whether a study will conform to the predetermined criteria for a meta-analysis. The final list of studies is then generated.

6.1.3 Data-extraction

Some authors recommend that a data-extraction document is drawn up in advance (CRD 1996) however, others argue that where systematic reviews are essentially "data-driven" rather than "question driven" then it makes more sense to compile the data extraction documentation as the data are uncovered. The important element is to ensure that all data are extracted so that studies can be examined critically and bases for comparison established. Although studies will have been selected for their similarities in patients and interventions, it does not follow that all studies will have used the same outcome measures. Rather than using a simple data extraction (as shown at Appendix 2) it is better to construct detailed data extraction tables to organise the data on each aspect of the studies under review. In this way, aspects such as trial design, input criteria, outcomes measured, can be displayed. Data can be entered directly in to a computerised database, such as Minitab or Access and may then be readily modified for analysis.
This also provides an opportunity to compare studies and check for obvious heterogeneity. At this stage it may become clear that pooling of the results by means of meta-analysis is not valid or sensible.

6.1.4 Data analysis and presentation

6.1.4.1 Dichotomous results

The first step in a meta-analysis is to find a consistent way of describing the results from each trial. One of the most common approaches is to "dichotomise" the results, that is, to turn them into yes/no, cured/not cured, died/survived format which can then be manipulated in a number of ways. Although many trials do not have results presented in this way, there are often sufficient data in the published report to make it possible. A clear understanding of the clinical issues is important to ensure that logical cut-off values are used.

Example: In a controlled trial of a new psoriasis treatment, the results may be presented as mean decreases in PASI score for the control and test groups. If sufficient information were given it would be possible to dichotomise the results - into 'cleared' or 'not cleared' categories for each treatment group. First it would be necessary to decide on a suitable cut-off value for the PASI. A

reduction of 75% from baseline or a reduction to a value of less than 8 would make sense in a clinical situation and would be consistent with values used in published studies. The results could now be shown as the numbers in each group which did/did not achieve the cut-off value.

6.1.4.2 Risk ratio versus odds ratio

Risk describes the probability that an event will occur (the number of subjects who experience the event / the total number in the group). Conventionally, 'risk' is a term related to adverse effects but the concept can also be applied to beneficial events and, in this case, is more often described as a 'rate'. Odds describe the probability that an event will occur against the probability that it will not occur.

Example:

Table 6.1: Effect of antenatal steroid for prevention of respiratory distress syndrome (RDS) (Morales WJ 1986)

In the example shown, the risk of RDS in the control group is 0.51 whereas the odds of developing RDS are 1.03. Odds may be converted to risk using the relationship:

$$\text{Risk} = \text{Odds}/(1+\text{Odds})$$

but this is rarely done. (Sinclair 1994)

The relative risk (RR) (or risk ratio, event rate ratio) describes the relative probability that an event will occur when two treatment groups are compared. In this example, the relative risk of RDS is given by (30/121)/(63/124) = 0.49. The relative risk reduction (RRR) is given by (1- relative risk). In this example the RRR is 0.51 which means that there is a 51% reduction in RDS in the treated group compared to the control group.

The odds ratio (OR) describes the odds of an event in the treated group compared with the control group. In the example the odds ratio is 30:91/63:61 = 0.32. The relative odds reduction (ROR) is given by (1-odds ratio).

The odds ratio can be converted in to a risk ratio, but because the ratio is a comparison of two groups, a term for the incidence of the event in the control group is also required:

$$\text{Risk ratio} = \frac{OR}{1 + I_c(OR - 1)}$$

where I_c = incidence of the event in the control group

6.1.4.3 Relative and absolute estimators of effect

The risk difference (absolute risk reduction, ARR) describes the absolute difference in event rates between treated and control groups. In the example this is 0.25 - 0.51 = -0.26, that is, the absolute risk of RDS is reduced by 26% as a result of steroid treatment. The reciprocal of risk difference (1/risk difference) gives the number of patients that need to be treated (NNT) in order to prevent one event (although the calculation is only valid if the confidence interval around the RD is relatively narrow) In the example, the NNT is 1/0.26 = 4.

Where the outcome of a trial is an increase in a positive effect rather than a decrease in a negative effect, the risk difference is sometimes described as the "absolute benefit increase'. This is explored in more detail in Chapter 11.

Table 6.2: Relative and absolute estimators of effect

Estimator	Abbreviation	Question answered
Relative risk (risk ratio)	RR	What is the proportion of treated patients, relative to control patients who experience an event?
Odds ratio	OR	What are the odds of the event occurring in the treated patients relative to the odds of its occurring in control patients?
Relative risk reduction	RRR	By how much in relative terms is the event rate reduced?
Absolute risk reduction or absolute benefit increase (risk difference)	ARR or ABI (RD)	What is the absolute difference in event rates between the treated and control groups?
Number needed to treat	NNT	How many patients need to be treated to prevent one patient from experiencing an event?

The odds ratio and the risk ratio give similar results where the risks are small, that is less than approximately 20%. (Thompson 1991) Above this value the two estimators diverge. The odds ratio is used to provide an approximation of relative risk in case-control studies, in which patients and controls are selected because they have or do not have the outcome of interest. Laupacis and colleagues observed that the odds ratio has become the preferred statistic for pooling data across trials in meta-analyses, partly because of the simplicity of statistical methods. (Laupacis 1988)

6.1.4.4. Pooling methods - random and fixed effects models

Dichotomous data can be pooled using random or fixed effects models. The differences between the two models are summarised in Table 6.3.

Table 6.3: Random and fixed effects models for meta-analysis (after Petitti 1994, Egger 1997)

The choice of model for analysis is linked to the degree of inter-study variance (heterogeneity). If studies are homogeneous (i.e. there is no interstudy variance) then both methods will yield identical results, however, if they are heterogeneous then the random effects model should be used. The random effects model is relatively conservative and produces estimates with wider confidence intervals, (Berlin 1989) however, it may also give undue weight to small trials. (Thompson 1991)

6.1.4.5 Heterogeneous data

If the results of trials are very different then it may not be appropriate to combine them. A statistical test of heterogeneity is often used as the deciding factor. This procedure tests whether results reflect a single underlying effect or a distribution of effects. Although this is superficially elegant, the main drawback is that this type of test lacks power (i.e. it may fail to reject the null hypothesis that results are homogeneous even when substantial differences exist). The identification of heterogeneity should not merely prompt the use of a random-effects model, but should also lead to a critical search for an explanation. This may lie in features of trial design, characteristics of patients included or other clinically-relevant aspects of a trial. (Bailey 1987, Thompson 1991, Thompson 1994) Indeed Jenicek cautions, " it is better to analyse differences and to draw new hypotheses and test them rather than to try to obtain some universal protective ratio which applies to neither group in the original studies."

6.1.4.6 Sensitivity analysis

Because a number of methods of meta-analysis could be applied to most groups of studies, it is important to examine the robustness of the results by means of a sensitivity analysis. This process involves repeating the analysis whilst making small changes. (Greenhouse 1994) In this situation this could involve using both fixed effects and random effects models to calculate the overall result and, for example, checking the effect of removing trials of doubtful quality, small trials, trials of shorter/longer duration.

6.1.4.7 Publication bias

Publication bias is the systematic error induced in a statistical inference by using only published trials in an analysis. The error arises because research with significant (and usually positive) results is more likely to be submitted and published than studies with null or non-significant results. Published studies, therefore, are not representative of all the studies which have been performed in a given area. One method of checking for the presence of publication bias is to construct a "funnel plot". (CRD 1996) This is done by plotting sample size against effect size (typically as an odds ratio or risk ratio). It is expected that the points will fill an inverted funnel shape. Large gaps in the funnel shape may indicate "missing" studies. Characteristically the missing points will correspond to negative trial results. Figure 6.2 shows examples of two situations. The right-hand plot shows a clear inverted funnel shape. In this case the effect size obtained by meta-analysis of the available trials was very close to the value obtained in subsequent large trials. The left-hand plot is less obviously funnel-shaped, which raises the possibility that trials with negative results are missing. The pooled effect size obtained by meta-analysis was strongly positive, suggesting that intravenous magnesium was more efective than streptokinase in preventing deaths due to myocardial infarction. A later large trial (ISIS-4) refuted this hypothesis.

Figure 6.2:

Funnel plots for meta-analyses refuted and confirmed by subsequent mega-trials: intravenous magnesium (left) and streptokinase (right) in acute myocardial infarction

(Egger 1995)

6.2 Meta-analyses of treatments for severe psoriasis - methods

6.2.1 Objective and search strategies

6.2.1.1 Objective

The objective of the meta-analyses was to evaluate the comparative efficacy and tolerability of oral treatments and PUVA for severe psoriasis through systematic reviews of randomised controlled trials. Only trials for moderate-severe, chronic plaque psoriasis were included. Trials for guttate psoriasis, palmo-plantar-pustular psoriasis and erythrodermic psoriasis were excluded.

6.2.1.2 Selection criteria

A broad search strategy was used initially in an attempt to identify all the studies concerned with treatment of severe psoriasis. Specific drug or treatment terms were used after this stage and finally randomised, controlled studies were extracted from the database and used for the review. Studies in all languages were included.

6.2.1.3 Search strategy

Medline (1966 to June 1999) and Embase (1980 to June 1999) searches were conducted using the terms 'psoriasis' and 'treatment' and 'psoriasis-drug-therapy'. The additional terms, 'study', 'trial*', 'random*' in the text, 'compar*' in the title and 'clinical-trial' in the subject heading were used to increase the specificity of the search. The subject terms were then inserted, for example, 'cyclosporin*' or ciclosporin' was then used to locate trials concerned with cyclosporin use.
The Cochrane register of randomised controlled trials was searched for trials involving specific treatments and psoriasis.
Manufacturers were approached to identify additional studies. Recent conference proceedings were hand-searched. Recent issues of key dermatology journals 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.

6.2.1.3 Data extraction

All potentially comparable input and outcome data were extracted and recorded in tables using Minitab® software v. 10.2, 1994 (Minitab Inc USA). In this way a consistent dataset was identified and used to compile the tables that show the design and outcomes of the trials under review. The numbers of patients enrolled in the trials were extracted so that all analyses for this project could be performed on an 'intention-to-treat' basis. This was done by calculating the success rates for each

trial as a proportion of the total number of patients enrolled rather than the number of patients who completed the trial.

6.2.1.5 Statistical analysis - Outcome measures

The PASI score is frequently used to assess the outcome of psoriasis treatment but it was not used for all of the RCTs included in the following overviews. 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 other 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 inter-converted using the information available in the published papers. Although the PASI initially appeared to be the most satisfactory outcome measure, its use for analysis would have resulted in the loss of too much information to make it useful.

Another common approach in this situation is to find a way to dichotomise the results (i.e. turn then 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. Tables in chapters 7, 8 and 10 show the criterion adopted by each study for success. The most widely used criterion was a decrease in PASI score of at least 75% or a decrease to an absolute value of 8 or less. It was assumed that this would correspond to the category of "clear or almost clear" used by Ellis (Ellis 86, Ellis 91) and other authors. The benefit of this approach is that it reflects the way in which patients assess the effectiveness of treatments, that is to say, they either clear the condition or they do not. It is well known that it is possible for a trial to show statistically significant changes that are clinically insignificant and this approach avoids the risk of including this type of result. The potential weaknesses of the approach are that small differences on the original scale may be magnified by dichotomising the data and that the results can be influenced by the use of different cut points. The worst possibility is that trialists choose the cut point after seeing the results rather that using a protocol-defined cut point. In the case of psoriasis, the cut-point (75% decrease in PASI or absolute value below 8) is widely recognised and commonly included as an a priori outcome measure.

Several statistical methods exist to derive pooled estimates of effects from dichotomous data. In this study, both odds ratios and risk differences have been used. The risk difference is needed in order to calculate the number needed to treat (NNT) (see Chapter 11).

Odds ratio

The Mantel-Haenzsel method (Petitti 1994) or Peto method (Petitti 1994) can be used to calculate an odds ratio after a 2x2 table has been constructed for each trial in the overview.

Table 6.4: Arrangement of data for Mantel-Haenzsel (MH) method and Peto methods

	TREATED	NOT TREATED	TOTAL
Diseased	a	b	g
Not diseased	c	d	h
Total	e	f	n

The odds ratio for the trial is then, $\frac{a \times d}{b \times c}$

The MH pooled odds ratio (OR_{mh}) is calculated as

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

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

The 95% confidence interval for the odds ratio is derived from the standard error of the logarithm of odds ratio, which is given by

SE (ln OR) =

$$\sqrt{\frac{1}{a} \oplus \frac{1}{b} \oplus \frac{1}{c} \oplus \frac{1}{d}}$$

The 95% confidence interval for the log odds ratio is therefore

ln OR – 1.96 x SE (ln OR) to ln OR + 1.96 x SE (ln OR).

The 95% confidence interval for the odd ratio is therefore from $e^{\text{lower limit}}$ to $e^{\text{upper limit}}$.

This is described in full by Altman (Altman 1991)

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. (Shadish 1994). For the analyses in this project, this procedure was followed.

Several formulae exist to calculate a statistic (Q) that is used to test for homogeneity. The general principle is to calculate the sum of the weighted difference between the summary effect measure and the measure of effect from each individual study. The resulting value is referred to the Chi-square distribution. The number of degrees of freedom is equal to the number of studies minus one. If the value is greater than the cut-off value for the selected p-value (usually 0.05) then the null hypothesis of homogeneity is rejected.

For the Mantel-Haenszel method the calculation is:

$Q = \text{sum}\,[\text{weight}_i \times (\ln OR_{mh} - \ln OR_i)]$

(Pettiti 1994, Chapter 7)

For estimations of effect size pooled odds ratios were calculated using the Mantel-Haenszel (fixed effects) method when data were not heterogeneous; the DerSimonian & Laird (random effects) methods was used for heterogeneous data (Petitti 1994).

Rate difference

Rate differences (also known as risk differences, absolute benefit increases and therapeutic gain) were also calculated. A pooled rate difference can also be calculated as a summary measure of effect.

Summary rate difference (RD_s):

$$RD_s = \frac{\text{Sum}\,(\text{weight}_i \times RD_i)}{\text{Sum}\,(\text{weight}_i)}$$

Where

$\text{Weight}_i = 1/\text{variance}_i$

Variance (v_i) of a rate difference = $p_{i1}(1- p_{i1})/ n_{i1} + p_{i2}(1- p_{i2})/ n_{i2}$

where p_{i1} and p_{i2} are the proportions of individuals in the experimental and control groups who have the condition (treatment success); rate difference = $(p_{i1} - p_{i2})$

Homogeneity is tested using the Q statistic:

$$Q = \text{Sum}\,[\text{weight}_i \times (RD_s - RD_i)^2]$$

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

The 95% confidence interval for the pooled estimate is given by

$$RD \pm (1.96 \sqrt{\text{variance}_s})$$

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

This described in detail by Petitti (Petitti 1994)

Relative risk

For estimations of the relative risk of withdrawal from trials due to side effects the risk ratio was calculated (when sufficient data could be extracted from the trial reports).

Meta-analyses were performed using Intercooled Stata 6.0 for Windows (Stata Corporation, Texas).

Chapter 7

Systematic review of trials of oral cyclosporin

Summary

Nineteen eligible RCTs, were located for this review. Fourteen were concerned with induction of remission and five with maintenance treatment. The trials are grouped according to the types of comparisons involved: placebo controlled trials of cyclosporin; comparisons with retinoids; comparisons of dose levels; cyclosporin in combination with calcipotriol and comparisons of cyclosporin formulations. The results of similar trials were pooled using different measures of effect size and both fixed and random effects models. A meta-regression analysis showed a relationship between dose and effect size. Potential sources of heterogeneity are identified.

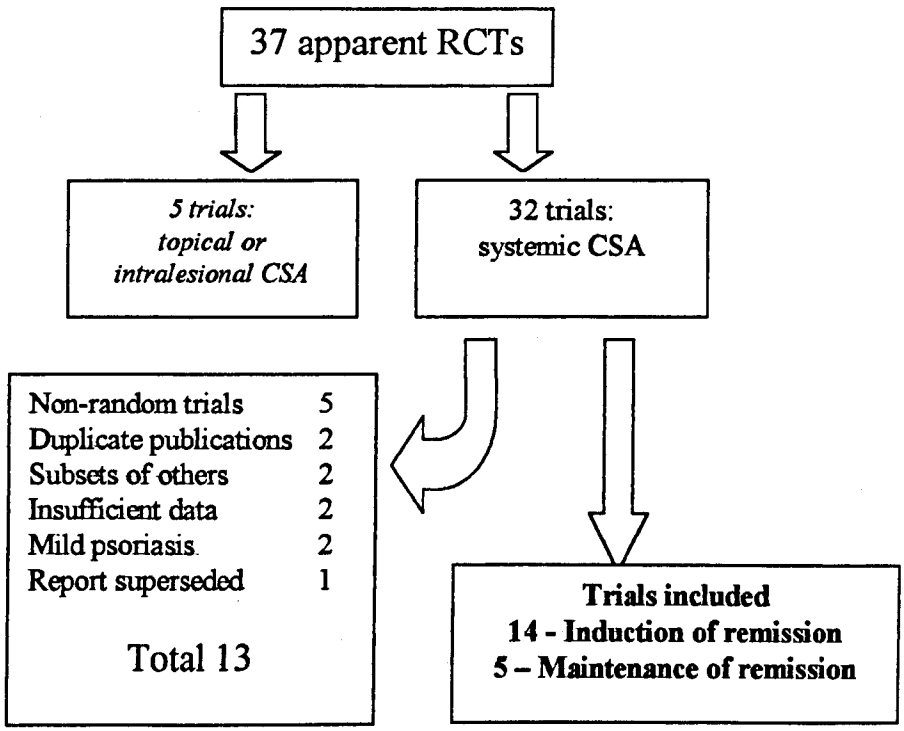
7.1 Search results

Trials of oral cyclosporin were identified using the search strategy described in Chapter 6. This identified 169 citations. Of these, 88 were reports of therapeutic trials, including randomised controlled trials, controlled trials (non-randomised), cohort studies, retrospective studies, case reports & small series. Titles and abstracts were reviewed by two people independently (the author and a consultant dermatologist) to identify randomised controlled trials (RCTs). Thirty-seven records appeared to be reports of RCTs and of these, 31 concerned the use of systemic cyclosporin and five concerned the use of topical cyclosporin. All of these were retrieved and read.

Eighteen studies were excluded from the final review (see Table 7.1) Two of the reports were duplicate publications (Bagot 1994/Grossman 1994; Mrowietz 1991/Christophers 1992) two were subsets (Bayerl 1992, Schulze 1991) of a multicentre study (Mahrle 1995) and five were non-randomised studies.(Blaszczyck 1997, Gottlieb 1995, Kokelj 1997, Timonen 1995, Wanqing 1995) One had been superseded by a later, more detailed report. (Nakayma 1996) These ten reports were excluded from the final list along with the five reports of topical or intralesional cyclosporin.(Baykal 1994, Bunse 1990, Gajardo 1994, Ho 1990, Petronic-Rosic 1997)

Studies included in the final review were restricted to those which were concerned with the treatment of moderate-severe or severe psoriasis and which contained sufficient data for analysis. Three studies, which failed to meet these criteria, were excluded. (Levell 1995, Dubertret 1989, Engst 1989)

Figure 7.1: Flow chart to show cyclosporin trials excluded



The final list contained nineteen randomised trials of cyclosporin; fourteen were concerned with the induction of remission and five were concerned with maintenance treatment. These are summarised in Tables 7.4 and 7.5.

Table 7.1 Cyclosporin (CSA) trials excluded

	First author and year of publication	Reason for exclusion
1	Bagot 1994	Same data as Grossman 1994
2	Bayerl 1992	Data are a subset of Mahrle 1995
3	Baykal 1994	Intralesional cyclosporin
4	Blaszczyk 1997	Not a randomised study of CSA. CSA used in non-randomised pre-study phase
5	Bunse 1990	Topical cyclsoporin
6	Dubertret 1989	Insufficient data for analysis
7	Engst 1989	Insufficient data for analysis
8	Gajardo 1994	Topical cyclosporin
9	Gottlieb 1995	Non-randomised study
10	Ho 1990	Intralesional cyclosporin
11	Kokelj 1998	Non-randomised study
12	Levell 1995	Mild-moderate psoriasis
13	Mrowietz 1991	Same data as Christophers 1992
14	Nakayama 1996	Report superseded by more detailed report (Ozawa 1999)
15	Petronic-Rosic 1997	Intralesional cyclosporin
16	Schulze 1991	Data are a subset of Mahrle 1995
17	Timonen 1990	Non-randomised study
18	Wanqing 1995	Non-randomised study

7.2 Description of Trials

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. Table 7.4 shows that the trials differ considerably with respect to four main variables, namely, initial severity of disease, cyclosporin dose, success criterion and duration of treatment and it is likely that these differences account for the marked variations in success rates although other factors, such as interacting drugs or variable compliance with the dosage regimens cannot be excluded.

The severity of disease was described in several ways. In seven of the trials, a threshold level of the Psoriasis Area and Severity Index (PASI) was used, usually in conjunction with other, secondary criteria (such as percentage of body surface area affected, failure to respond to at least one other systemic treatment or prolonged duration of disease). Two trials expressed disease severity as percentage of body surface area affected and used threshold values of 20% and 25% (Ellis 1986, Ellis 1991) and the remainder simply described the disease as 'moderate-to-severe' or 'severe'. The threshold levels for the PASI ranged from 8 to 20.

The criterion for success was expressed as a change in the PASI score for 10 of the trials. The remaining two 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 used a decrease in PASI of 50% as the criterion for success and reported a successful outcome in 11 out of 12 patients (92%) (Guenther 1991). At the other end of the scale, Grossman used a 90% decrease in PASI as the success criterion and reported a successful outcome in 4 out of 34 (12%) patients (Grossman 1994). Meffert used a success criterion of 75% decrease in PASI but included patients with PASI scores as low as 8 (Meffert 1997). These authors reported successful outcomes in 4 of 41 (10%) and 12 of 44 (27%) patients on daily doses of 1.25 mg/kg and 2.5 mg/kg respectively.

The dosage of cyclosporin ranged from 1.25 mg/kg/day to 14 mg/kg/day. Two patient series received doses of 1.25 mg/kg/day and achieved successful outcomes in 4 out of 41 (10%) and 7 out of 36 (18%). Six patient series received doses of 5.0 or 5.5 mg/kg/day and achieved successful outcomes in 50-97% of patients.

The duration of treatment ranged from 4 weeks to 12 weeks. This may also account for some of the variability of the results. Trials which have reported cumulative success rates (e.g. Koo 1998) have shown that the response curve does not level until 12 or 16 weeks, which suggests that trials which ended earlier are likely to show variable results.

Table 7.5 shows the outcomes of trials of cyclosporin for maintenance of remission. Two trials (Ellis 1995 and Shupack 1997) compared two doses of cyclosporin with placebo. Ozawa compared intermittent and continuous dosing (Ozawa 1999) and Zachariae compared two formulations of cyclosporin (Zachariae 1998). The success criteria were slightly different for each study. Ellis used an increase of no more than two points on a global assessment scale (Ellis 1995), Ozawa used an increase to no more than 50% of the pre-study baseline PASI score (Ozawa 1999), Shupack used an increase to no more than 50% of the pre-study baseline body surface area affected (Shupack 1997) and Zachariae used an increase of less than 8 in the PASI score or an increase of less than two points in a global score (Zachariae 1998). The doses of cyclosporin also varied between 1.5 and 5mg/kg/day. In the placebo-treated groups the proportions of subjects remaining in remission at the conclusion of the trials were 5% (Ellis 95) and 16% (Shupack 97)

7.3 Comparative efficacy of cyclosporin

7.3.1 Induction of remission

Cyclosporin compared with placebo

In total, 298 patients participated in six placebo-controlled trials of cyclosporin. All except two trials (one using a low dose of 1.25 mg/kg/day and one with only 6 subjects in each group) showed a positive odds ratio (favouring cyclosporin). (see table 7.4, figure 7.2) The pooled odds ratio (random effects) was 18.36 (95% CI 5.35 – 62.96). The trials differed considerably with respect to four main variables, namely, initial severity of disease, cyclosporin dose, success criterion and duration of treatment.

Cyclosporin compared with etretinate

Two trials involving 286 patients compared cyclosporin with etretinate. In each trial cyclosporin was significantly more effective then etretinate (ORs 13.28, 95% CI 1.62 – 109.00 and 8.80, 95% CI 4.25 –18.25). The pooled OR (fixed effects) was 9.34 (95% CI 4.69 - 8.62). Although the two trials used very different doses of cyclosporin and etretinate (see Table 7.4 and Figure 8.6), there was no statistical evidence of heterogeneity.

Calcipotriol and cyclosporin

One trial (69 patients) compared low-dose (2.0 mg/kg/day) cyclosporin and calcipotriol with cyclosporin and placebo ointment. The trial had a very strict success criterion (> 90% reduction in PASI) and yet, at six weeks, the combination was significantly better than cyclosporin alone (OR 7.08, 95% CI 2.06 – 24.38).

Cyclosporin dosage comparisons

Three trials (Christophers 92, Laburte 94, Meffert 97) involving 553 patients, provided patient series in which different doses of cyclosporin were compared. The results showed that, at 12 weeks, 5mg/kg/day was significantly superior to 2.5mg/kg/day (pooled OR 3.52, 95% CI 2.30 – 5.36). At 10-12 weeks 2.5mg/kg/day was significantly superior to 1.25mg/kg/day (pooled OR 3.86, 95% CI 1.87 - 7.96).

Cyclosporin formulation comparisons

Two trials (382 patients) compared the traditional cyclosporin formulation (Sandimmun®) with the newer micro-emulsion (Neoral®). Neither trial showed any difference between the two products in terms of success rates at 12 weeks. The pooled odds ratio was 1.16 (95% CI 0.68 - 1.97)

7.3.2 Maintenance of remission

Cyclosporin compared with placebo

Two trials (202 patients) compared two different doses of cyclosporin (1.5 mg/kg/day and 3.0 mg/kg/day) with placebo in the maintenance treatment of psoriasis. Results were reported at 16 weeks and 24 weeks. The higher dose was significantly superior to placebo whereas the lower dose was not significantly different from placebo. At 16 weeks, the pooled odds ratio for the 3mg/kg/day dose compared with placebo was 8.37 (95% CI 3.97 -17.61)

Cyclosporin treatment schedule comparisons

Ozawa and colleagues compared continuously-dosed cyclosporin with intermittently-dosed cyclosporin for maintenance treatment. (Ozawa 1999) 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.

Analysis of their results shows that an average daily dose of 3.2 +/- 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 (+ topical steroids), delivered as intermittent therapy, kept patients in remission for 32% of time.

Cyclosporin formulation comparisons

The one study that compared the traditional and micro-emulsion formulations of cyclosporin (Sandimmun® and Neoral®) for maintenance treatment showed no significant difference in effectiveness over a 24 week period. (Zachariae 1998)

7.4 Withdrawal from treatment due to adverse effects or lack of efficacy

Amongst trials of cyclosporin for induction of remission of psoriasis, withdrawals from treatment because of side effects or lack of efficacy were reported in adequate detail in only five of the trials (Finzi 1993, Mahrle 1995, Koo 1998 & Guenther 1991, Engst 1989). One study reported only adverse effects in the cyclosporin-treated group (van Joost 1988). In other reports it was not clear when subjects had been withdrawn or from which group.

In the two trials comparing cyclosporin with etretinate (Finzi 93, Mahrle 95) withdrawals due to side effects or lack of efficacy were fully reported. The pooled risk ratio (fixed effects) for withdrawal was 0.78 (95% CI 0.30 – 2.01, Q= 0.2, p=0.658), which fails to demonstrate a difference in the risk of withdrawal due to side effects or lack of effect with cyclosporin treatment compared to etretinate treatment.

Studies of cyclosporin for maintenance of remission of psoriasis reported adverse effects in different ways.

Ellis (Ellis 1995) and Shupack (Shupack 1997) both compared cyclosporin with placebo. Ellis, in a 16-week study, reported that no patient demonstrated signs of important clinical side effects. In Shupack's 24-week study five patients were withdrawn from the group receiving cyclosporin 3.0 mg/kg/day due to "renal causes" (increased serum creatinine - 3, decreased creatinine clearance - 1 and decreased glomerular filtration rate - 1). They reported that 17% of those receiving cyclosporin 3.0 mg/kg./day and 10% of those receiving placebo showed new or worsening creatinine abnormalities. Nevertheless they reported that there was no overall worsening of the glomerular filtration rate.

Zachariae (Zachariae 1998) and colleagues compared Neoral® and Sandimmun® for continuous maintenance treatment of psoriasis over 24 weeks. There was one withdrawal in each group because of side effects or lack of efficacy. Raised serum creatinine levels (>130% baseline value)

were reported in 6/20 and 5/14 patients receiving Neoral® and Sandimmun® respectively. New-onset hypertension was reported in 3/20 and 1/14. These differences were not statistically significant.

Ozawa and colleagues compared intermittent and continuous dosing of cyclosporin. In their safety sample of 94 patients (50 continuous treatment, 44 intermittent treatment) three and two patients respectively, were withdrawn because of side effects of lack of efficacy. Other side effects occurred with similar frequency in both groups (hypertension - 21, raised blood urea nitrogen -17, raised creatinine [no definition given]- 9)

In a multicentre study involving 400 patients receiving cyclosporin intermittently, the authors concluded that there were no statistically significant changes in mean creatinine and diastolic blood pressure during the study. (Ho 99)

7.5 Sources of heterogeneity

This overview has demonstrated marked heterogeneity among the RCTs that have been conducted. The understanding of the sources of heterogeneity is recognised to be as important as performing a formal statistical analysis. (Thompson 1991, Bailey 1987) In terms of clinical understanding it may be more relevant. Identifiable sources of heterogeneity included initial severity of disease, cyclosporin dose, success criterion, duration of treatment and formulation of cyclosporin. Compliance and interacting drugs may represent further sources of heterogeneity.
In trials for induction of remission of psoriasis the duration of treatment ranged from four to 12 weeks. Trials which have reported cumulative success rates have shown that the response curve does not level out until after 12 or 16 weeks of treatment (Laburte 1994, Finzi 1993, Koo 1998) therefore any trial which reports results at less than 12 weeks is bound to show greater variability in outcomes. Three of the six placebo-controlled trials reported results at four weeks.

7.6 Meta-analysis of results

Meta-analyses of the results from trials of cyclosporin compared with placebo were performed using several different methods in order to test the robustness of the pooled values to fixed and random effects assumptions. (See Table 7.2) The results were displayed as forest plots. (See figure 7.2). The results were not unduly sensitive to changes from fixed to random effects models.

Table 7.2: Comparison of different methods of analysis for trials of cycloporin vs. placebo

Analytical method	**Effect measure**	**Pooled effect size (95% CI)**	**Q – test for heterogeneity [df = 8] (p)**
Fixed effects - Mantel-Haenszel	Odds ratio	12.84 (6.61 – 24.93)	18.33 (0.019)
Fixed effects - Mantel-Haenszel	Risk ratio	8.21 (4.50 – 14.98)	11.42 (0.179)
Fixed effects -	Rate (risk) difference	0.39 (0.32 - 0.46)	85.61 (0.000)
Random effects - DerSimonian & Laird	Odds ratio	18.36 (5.35 – 62.96)	18.33 (0.019)
Random effects - DerSimonian & Laird	Risk ratio	6.71 (2.96 – 15.22)	11.42 (0.179)
Random effects –	Rate (risk) difference	0.51 (0.28 – 0.74)	85.61 (0.000)

The use of different effect size measures did, howevere, throw up some differences. When effect size was measured by risk ratio (RR) and meta-analysed using either a fixed or random effects model, there was no statistical evidence of heterogeneity (Q values were below the cut-off value, the p value was greater than 0.05). However, when effect size was measured by odds ratio (OR) or by rate (risk) difference a lack of homogeneity was demonstrated. This was to be expected, in view of the clear evidence of methodological differences described above and suggests that a number of confounding factors may be present. The most obvious candidates were dose, duration of treatment, baseline severity and the success criterion. The fact that one of the three approaches failed to demonstrate heterogeneity serves to underline the importance of considering both the statistical and qualitative analyses of the data.

In view of the heterogeneity of the data set, the best estimate of effect size is given by a random effects model. Such models tend to give conservative estimates with wide confidence intervals. In

this case the odds ratio, estimated by the method of DerSimonian and Laird, is 18.36 (95% CI 5.35 – 62.96)

Figure 7.2 shows forest plots for trials of cyclosporin versus placebo, arranged by dose in ascending order. There is a hint of a dose-response relationship. The results for the trials by Guenther (Guenther 91) and Engst (Engst 89) appear to be outliers and it should be noted that Guenther used a low success criterion and the trial by Engst had only five participants in each group.

In order to test the influence of cyclosporin dose a meta-regression analysis was performed. This was a logistic regression using the logarithm of the dose ($\log_{dose}$) as the regressor. It showed that the dose contributed to the overall effect (coefficient 1.85 (CI 0.71 – 2.98) p=0.001).
Figure 7.3a-c show the relationships between the dose, observed effect size (as log OR) and predicted effect size (as predicted log OR) based on the regression equation.
Figure 7.3a shows the observed OR versus dose for all trials of cyclosporin compared with placebo (all doses). The points are widely scattered and, despite the strong statistical significance of the regression, the graph only weakly suggests that there might be a relationship between effect size (OR) and dose. However, a graph of raw data such as this is potentially misleading as it does not reflect the weights given to the different trials in the way that forest plots of meta-analyses do.
Figure 7.3b shows the predicted log odds ratio versus log dose. This illustrates the theoretical odds ratios that would be generated for given doses using the regression equation that best fits the data. In order to show visually how close this relationship is, the predicted log odds ratio was plotted aginst the logarithm of the observed odds ratio (Figure 7.3c). Had the variations in dose accounted for all the differences in effect size then the points on this graph should lie on a straight line. The fact that they do not suggests that other factors also contribute to the observed effect.

Further logistic regressions were carried out and no statistical relationship was found between duration of treatment and overall effect. Relationships between baseline disease severity and success criterion were not explored statistically. These undoubtedly represent a source of variation but the variation would arise from the way in which these measures were used by the clinicians conducting the studies. Although they appear to be clear objective measures, both "body surface area affected" and the psoriasis area and severity score require the physician who makes the assessment to estimate the proportions of body surfaces affected by psoriasis. Studies have shown that individual practitioners are reasonably consistent (little intra-individual variation) but that there is often marked inter-practitioner variation. (Marks 1989)

7.7 Sensitivity analysis

The sensitivity of the result to the removal of trials involving unusually high and low doses was tested. This showed that as such trials were removed from the analysis, the pooled effect size increased. Removal of the trials using the most extreme doses (1.25 mg/kg/day and 14 mg/kg/day) gave an odds ratio of 19.75 which is little different from the overall pooled value of 18.36. However, removal of the trials using doses of 2.5 mg/kg/day, increased the odds ratio for success with cyclosporin treatment to 40.03. Although this sounds dramatic, it should be remembered that the relationship between odds ratio and event rate (experimental event rate) is not linear. The relationship is approximately linear when the event rate is below 20%. It is clear from Table 7.4 that the experimental event rates ('success rate - intervention') are all above 35%. In this area of the event rate/odds ratio curve a small change in event rate causes a large change in odds ratio. Including only trials that used doses in the range 3.0 – 5.5 mg/kg/day, resulted in a pooled odds ratio for success of 29.60. This is a particularly important finding as this is the dose range that is currently recommended. Even given that the result is derived from only four trials involving a total of 117 patients and the associated confidence interval is very wide, it still demonstrates the strongly positive effect of cyclosporin compared to placebo in this condition. Overall, it is safe to conclude that estimated effect size is stable and is not changed markedly by the removal of trials using very unusually large or small doses.

Table 7.3 Effect of removing trials using high and low doses of cyclosporin

Sensitivity analysis	Effect measure (model)	Pooled effect size (95% CI)	Q – test for heterogeneity (p)
Removal of high (>7.5 mg) and low doses (<2.5 mg)	OR (fixed)	19.75 (8.61 – 45.32)	9.79 (0.134) [df = 6]
Removal of all doses except 3.0 – 7.5 mg/kg	OR (fixed)	40.03 (11.41 - 140.35)	3.63 (0.459) [df = 4]
Removal of all doses except 3.0 – 5.5 mg/kg	OR (fixed)	29.60 (7.42 - 118.04)	2.33 (0.506) [df = 3]

7.8 Conclusions

Cyclosporin is an effective treatment for moderate-severe psoriasis. Given the marked heterogeneity, both methodological and statistical, between trials it is difficult to give a precise estimate of the effect size. The odds ratio for success for the dose range 3.0 – 5.5 mg/kg/day was approximately 30. A further insight into the effect size is provided by the 'therapeutic gain' and the number needed to treat (NNT) which are described in Chapter 11.

The effect of dose was difficult to demonstrate with the available data. The prevailing clinical impression is that doses of less than 3.0 mg/kg are ineffective. It appears that a dose of 1.25 mg/kg/day is not effective but doses of 2.5 mg/kg/day and more are effective and there appears to be a dose-response relationship.

Cyclosporin was more effective than etretinate and no difference in the risks of withdrawal due to side effects or lack of efficacy was demonstrated.

There was no evidence that reformulation (to the micro-emulsion) changed the efficacy or side effects rates for cyclosporin treatment.

In general, information about side effects was scarce in the majority of studies reviewed (except for those mentioned in section 7.4) and so it has not been possible to give an accurate estimate of the range or frequency of side effects. The majority of the trials included in the review were of relatively short duration and it must be acknowledged that long-term observational studies would provide more reliable information about side effects.

Table 7.4: Features of trials of cyclosporin to induce remission of psoriasis

Reference	Intervention	Comp-arator(s)	Design & duration	Numbers (CSA/ comparator)	Inclusion criterion (disease severity)	Success criterion	Success rates Intervention :comparator	Weight [a](D&L) [b] (M-H)	Odds ratio (95% CI)
Cyclosporin vs. Placebo									
Ellis 86	CSA 14 mg/kg	PLO	DB, PG, 4 wks	11:10	BSA>20%	clear/almost clear	8/11:0/10	9.1[a]	51.00 (2.30 – 1129.95)
Ellis 91a	CSA 3 mg/kg	PLO	DB, PG, 8 wks	25:25	BSA>25%	clear/almost clear	9/25:0/25	9.7[a]	29.36 (1.60 – 539.27)
Ellis 91b	CSA 5 mg/kg	PLO	DB, PG, 8 wks	20:25	BSA>25%	clear/almost clear	13/20:0/25	9.6[a]	91.80 (4.86 – 1732.55)
Ellis 91c	CSA 7.5 mg/kg	PLO	DB, PG, 8 wks	15:25	BSA>25%	clear/almost clear	12/15:0/25	9.3[a]	182.14 (8.72 – 3805.76)
Engst 89	CSA 5 mg/kg	PLO	DB, PG, 4 wks	6:6	PASI >20	75% dec/< 8 PASI	3/6:1/6	10.6[a]	5.00 (0.34 – 72.77)
Guenther 91	CSA 2.5 mg/kg	PLO	DB. PG, 10 wks	12:11	PASI > 12	50% dec PASI	11/12:1/11	9.8[a]	110.00 (6.05 – 2001.32)
Meffert 97a	CSA 1.25 mg/kg	PLO	DB, PG, 10 wks	41:43	PASI 8-25	75% dec PASI	4/41:3/43	15.9[a]	1.44 (0.30 – 6.88)
Meffert 97b	CSA 2.5 mg/kg	PLO	DB, PG, 10 wks	44:43	PASI 8-25	75% dec PASI	12/44:3/43	17.0[a]	5.00 (1.30 – 19.25)
van Joost 88	CSA 5.5 mg/kg	PLO	DB, PG, 4 wks	10:10	NR	75% dec/< 8 PASI	7/10:0/10	9.0[a]	45.00 (2.01 – 1006.75)

Table 7.4 continued

Reference	Intervention	Comp-arator(s)	Design & duration	Numbers (CSA/ comparator)	Inclusion criterion (disease severity)	Success criterion	Success rates Intervention :comparator	Weight [a](D&L) [b] (M-H)	Odds ratio (95% CI)
Cyclosporin vs etretinate									
Finzi 93	CSA 5 mg/kg	ETR 0.75 mg/kg	DB. PG, 12 wks	36:40	PASI > 15	75% dec/< 8 PASI	35/36:29/40	12.1[b]	13.28 (1.62 – 109.00)
Mahrle 95	CSA 2.5 mg/kg	ETR 0.5 mg/kg	SB, PG, 10 wks	140:70	"moderate-severe"	70% dec PASI	87/140:11/70	87.9[b]	8.80 (4.25 – 18.25)
Cyclosporin in different doses									
Christophers 92a	CSA 2.5 mg/kg	CSA 1.25 mg/kg	NB. PG, 12 wks	121: 36	PASI > 15	75% dec PASI	60/121:7/36		
Christophers 92b	CSA.5 mg/kg	CSA 2.5 mg/kg	NB. PG, 12 wks	60: 121	PASI > 15	75% dec PASI	41/60:60/121	53.7[b]	2.16 (1.13 – 4.14)
Laburte 94	CSA 5 mg/kg	CSA 2.5 mg/kg	NB, PG, 12 wks	132: 119	NR	75% dec/< 8 PASI	117/132: 57/119	46.3[b]	5.09 (2.90 – 8.93)

Table 7.4 continued

Reference	Intervention	Comp-arator(s)	Design & duration	Numbers (CSA/ comparator)	Inclusion criterion (disease severity)	Success criterion	Success rates Intervention :comparator	Weight [a](D&L) [b] (M-H)	Odds ratio (95% CI)
Cyclosporin and topical treatments									
CSCG 91	CSA 5 mg/kg liq + PLO oint	Betnovate oint bd + PLO liq.	DB, PG, 4 wks	79: 79	PASI >20	Marked improvement	40/79:8/79	-	9.10 (3.88 – 21.38)
Grossman 94	CSA 2 mg/kg +Calcipotriol	CSA 2 mg/kg + PLO ointment	DB, PG, 6 wks	35:34	PASI > 20	90% dec PASI	17/35:4/34	-	7.08 (2.06 – 24.38)
Cyclosporin: comparisons of formulations									
Elder[36]	CSA neo 300mg	CSA sim 300 mg	DB, Xover (modified), 12 wks	18:19	PASI ≥ 12	marked improvement or clearance	16/18:16/19	6.8[b]	1.50 (0.22 – 10.22)
Koo 98[37]	CSA neo 2.5 mg/kg	CSA sim 2.5 mg/kg	DB. PG, 12 wks	152:156	PASI > 15	75% dec PASI	122/152: 122/156	93.2[b]	1.13 (0.65 – 1.97)

Key to tables: CSA – cyclosporin; CSAcont - cyclosporin - continuous treatment ; CSAint - cyclosporin - intermittent treatment; CSAsim - cyclosporin as Sandimmun®; CSAneo - cyclosporin as Neoral®; DB - Double blind; ETR – Etretinate; NB - Not blinded; NR - Not reported; PG - Parallel group; PLO – Placebo; * - 36 months treatment - minimum; mean = 46.0 +/- 3.4 months

Table 7.5: Features of trials of cyclosporin to maintain remission of psoriasis

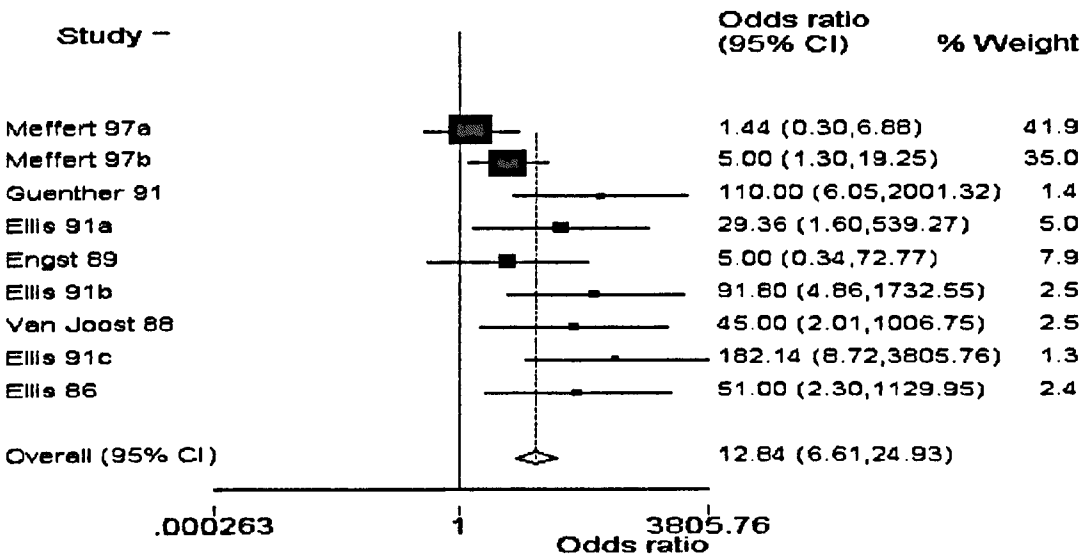
Reference	Intervention	Comparator(s)	Design & duration	Numbers (CSA/comparator)	Success criterion	Success rates Intervention: comparator	Weight	Odds ratio (95% CI)
Cyclosporin vs placebo								
Ellis 95a	CSA 1.5 mg/kg	PLO	DB, PG,16 wks	19:20	Increase of no more than 2 points on a 7-point scale	4/19:1/20		
Ellis 95b	CSA 3.0 mg/kg	PLO	DB, PG,16 wks	21:20	Increase of no more than 2 points on a 7-point scale	12/21:1/20	8.5	25.33 (2.84 –226.07)
Shupack 97a	CSA 1.5 mg/kg	PLO	DB, PG, 24 wks	7:49	Increase in body surface area affected to no more than 50% of baseline score	0/7:8/49		
Shupack 97b	CSA 3.0 mg/kg	PLO	DB, PG, 24 wks	86:49	Increase in body surface area affected to no more than 50% of baseline score	49/86:8/49 [57/86:11/49 at 16 weeks]	91.5	6.79 (3.03 – 15.21)

Table 7.5 continued

Reference	Intervention	Comparator(s)	Design & duration	Numbers (CSA/comparator)	Success criterion	Success rates Intervention: comparator	Weight	Odds ratio (95% CI)
Cyclosporin v: comparison of treatment schedules								
Ozawa 99	CSAcont 5 mg/kg	CSAint 5 mg/kg	NB, PG, 36 months*	17:20	Increase in PASI to no more than 50% of baseline score		N/A	N/A
Ho 99	CSA 2.5-5mg/kg, abruptly discontinued	CSA 2.5-5mg/kg, dose gradually discontinued	NB,PG, 12 mths	192:173	Increase to no more than 75% of pre-treatment disease extent		N/A	N/A
Cyclosporin: comparisons of formulations								
Zachariae 98	CSAneo 3 mg/kg	CSAsim 3 mg/kg	NB, PG, 24 wks	28:30	Increase of no more than 2 points on a global scale or increase in PASI score to no more than 8	19/28: 18/30	N/A	1.41 (0.48 – 4.14)

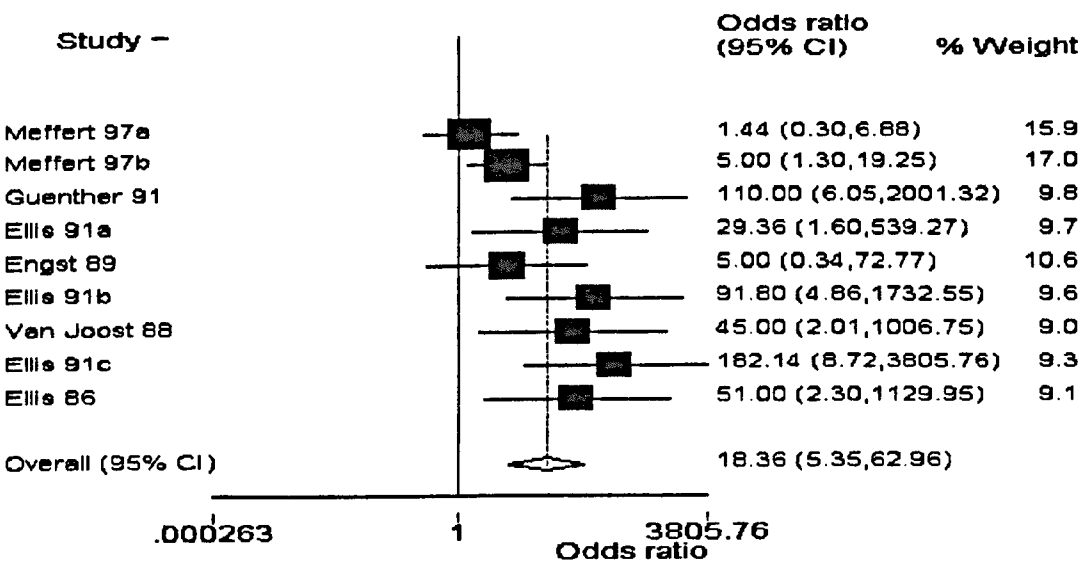
Figure 7.2: Forest plots showing odds ratios of trials of cyclosporin (all doses, in ascending order by dose) vs. placebo analysed by random and fixed effects methods

Fixed effects (Mantel-Haenszel)



M-H pooled OR 12.8363 (6.61011 - 24.9272)
Heterogeneity chi-squared = 18.33 (d.f. = 8) p = 0.019
Test of OR=1 : z= 7.54 p = 0.000

Random effects (DerSimonian &Laird)



D+L pooled OR 18.3568 (5.35235 - 62.9577)
Heterogeneity chi-squared = 18.33 (d.f. = 8) p = 0.019
Estimate of between-study variance Tau-squared = 1.8568
Test of OR=1 : z= 4.63 p = 0.000

Figure 7.3a: Odds ratio for success versus dose for trials of cyclosporin vs. placebo (all doses). This shows the actual calculated odds ratio for each trial plotted against the dose of cyclosporin.

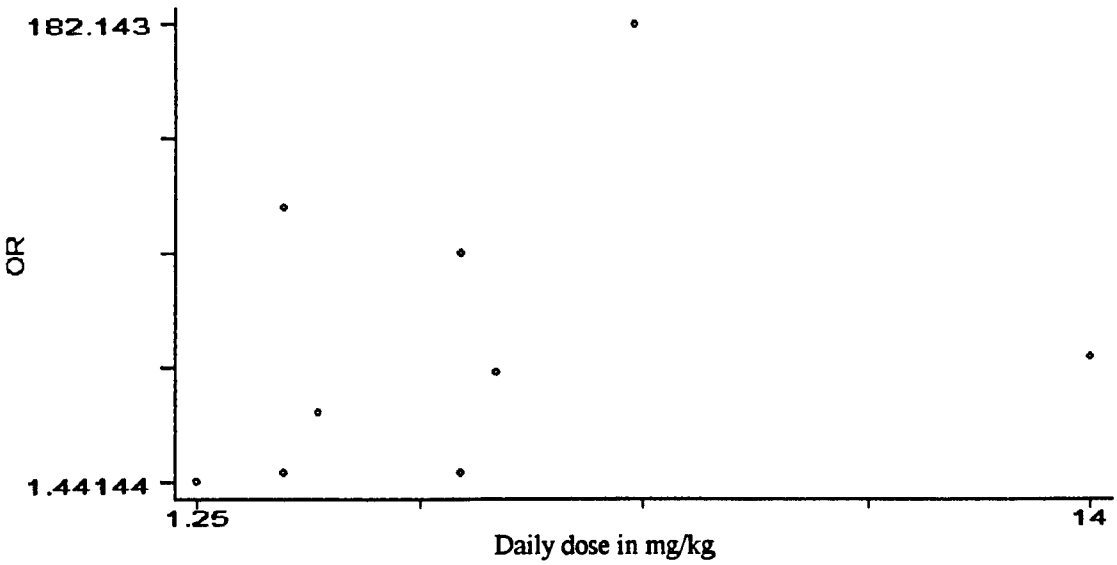


Figure 7.3b: Predicted log odds ratio versus log dose for trials of cyclosporin vs. placebo (all doses) This illustrates the theoretical odds ratios that would be generated for given doses using the regression equation that best fits the data.

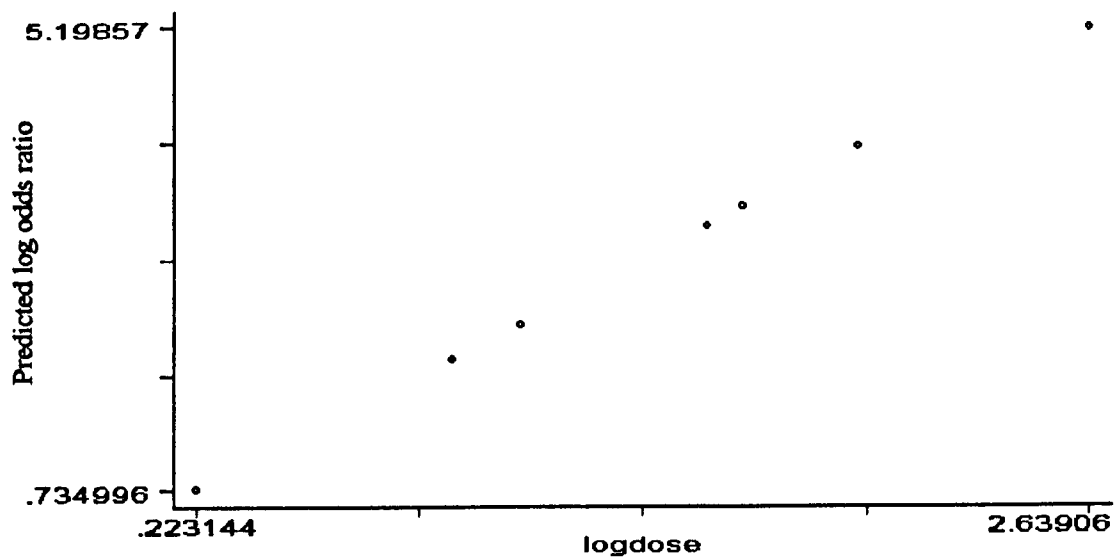
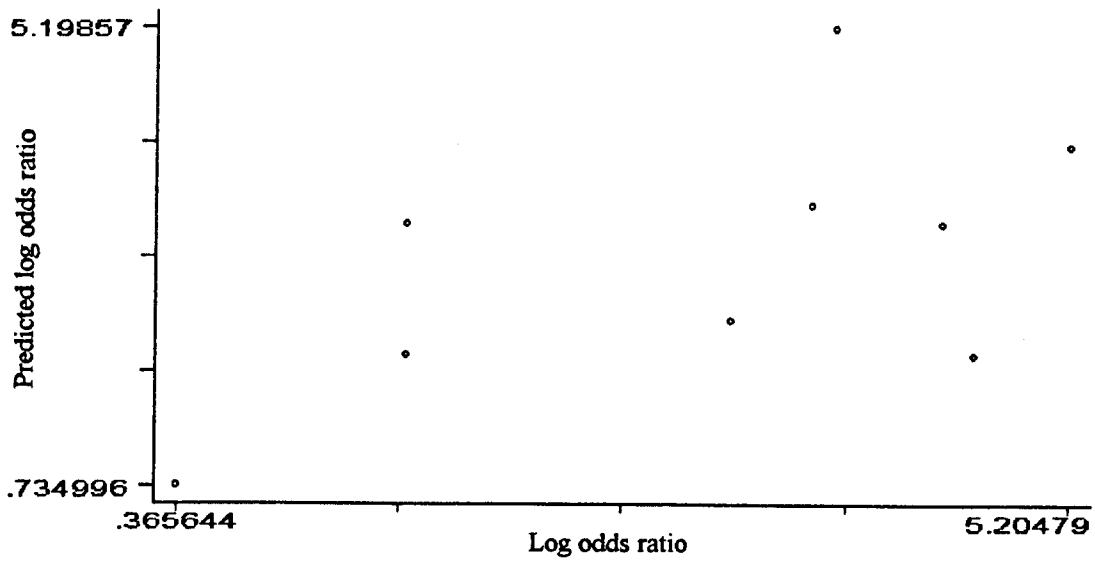


Figure 7.3c Predicted log odds ratio versus the logarithm actual odds ratio for trials of cyclosporin vs. placebo (all doses). If variations in dose accounted for all the differences in effect size then the points on this graph should lie on a straight line. The fact that they do not suggests that other factors also play a role.



Chapter 8

Systematic review of trials of oral retinoids

Summary

Thirty-three eligible RCTs, were located for this review. The trials are grouped according to the seven different types of comparisons involved: placebo controlled trials of retinoids; comparisons of acitretin with etretinate; comparisons involving retinoid-PUVA combinations; comparisons involving retinoid-UVB combinations; comparisons involving retinoid-topical treatment combinations; comparisons of etretinate with cyclosporin and comparisons of different dosage schedules for acitretin. The results of similar trials were pooled using different measures of effect size and both fixed and random effects models. Potential sources of heterogeneity are identified.

8.1 Search results

Trials of oral retinoids were identified using the search strategy described in Chapter 6. One hundred and seventy-nine 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 & small series. Titles and abstracts were reviewed by two people independently (the author and a consultant dermatologist) to identify RCTs. Fifty-seven citations appeared to be reports of RCTs and of these, 31 concerned the use of etretinate, 24 concerned the use of acitretin, one the use of topical 13-cis-retinoic acid and one the use of tazarotene. All of these were retrieved and read.

Twenty-four studies were excluded from the final review (see figure 8.1, table 8.1) Twelve were 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. Three were not prospective studies (one editorial and two large case series). These 22 reports were excluded from the final list along with the reports of topical treatment with 13-cis-retinoic acid or tazarotene. Thirty-three RCTs were therefore available for inclusion in this review.

Figure 8.1: Flow chart to show retinoid studies excluded

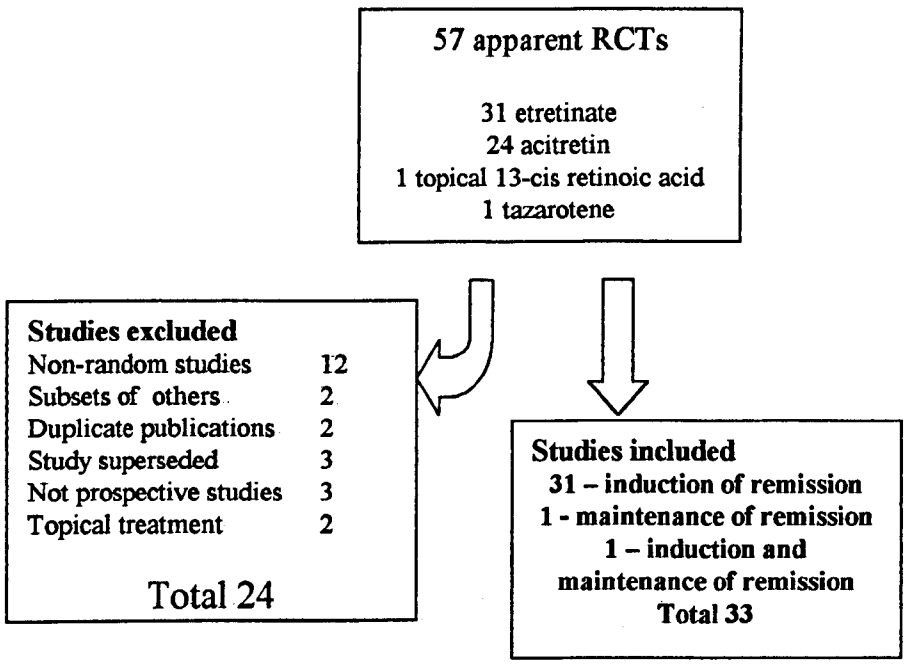


Table 8.1: Retinoid trials excluded

	First author and year of publication	Reason for exclusion
1	Bayerl 1992	Data area subset of Mahrle 1995
2	Bergner 1991	Same data as Ruzicka 1990
3	Bjerke 1989	Data published in full later
4	Bischoff 1992	Topical retinoic acid
5	Darouti 1988	Non-randomised study
6	Goerz 1978	Non-randomised study
7	Gollnick 1983	Large case series
8	Gruca 1984	Same data as Jacubowicz 1987
9	Gupta 1989	Data published in full later
10	Koh 1995	Non-randomised study
11	Lane Brown 1987	Non-randomised study
12	Langner 1995	Non-randomised study
13	Lawrence 1983	Data published in full later
14	Murray 1991	Non-randomised study
15	Orfanos 1979	Large case series
16	Park 1987	Non-randomised study
17	Rosinska 1987	Non-randomised study
18	Schulze 1991	Data area subset of Mahrle 1995
19	Snodgrass Cowart 1982	Editorial
20	Sonnichsen 1983	Non-randomised study
21	Stern 1995	Non-randomised study
22	Takashima 1988	Non-randomised study
23	Weinstein 1997	Mild-moderate psoriasis
24	Wanqing 1995	Non-randomised study

8.2. Description of trials

The thirty-three trials included in the review fell into seven categories (summarised in tables 8.2 – 8.8):

- comparisons of retinoids with placebo (Table 8.2)
- comparisons of acitretin with etretinate (Table 8.3)
- comparisons of retinoid-PUVA combinations with other treatments (Table 8.4)
- comparisons of retinoid-UVB (broadband and narrowband) combinations with other treatments (Table 8.5)
- comparisons of retinoid-topical treatment combinations with other treatment (Table 8.6)
- comparisons of etretinate with cyclosporin (Table 8.7)
- comparison of different dosage schedules for acitretin (Table 8.8)

8.2.1. RCTs of retinoids 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. Thirteen trials concerned the use of etretinate, 11 acitretin and a further eight were comparisons of the two drugs, either alone or in combination with PUVA (the combination known as 'RePUVA'). As with the cyclosporin trials, there were considerable variations in the initial severity of the disease, drug (retinoid) dose, success criterion and duration of treatment. Other factors which may have contributed to the variability in the results were the mix of patients (according to disease and gender) and compliance with the dosage regimens. Although trials involving patients with chronic plaque psoriasis were selected (and those involving exclusively palmo-plantar pustular psoriasis were excluded) several series contained a small number of patients with palmo-plantar pustular psoriasis. One study specifically included patients with guttate psoriasis. (Green 1992) As expected, in view of the documented teratogenicity of oral retinoids, the trials included a majority of male patients, although specific exclusions for fertile females were not consistently reported.

Twelve of the 31 trials for induction of remission of psoriasis used an objective disease severity criterion for inclusion. Eleven of these were a threshold value for the percentage of body surface area affected (range 5-20%) and one was a threshold PASI value (>15). The remainder of the studies gave a description, for example, "severe psoriasis", "extensive psoriasis" or "longstanding psoriasis" except for two 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 30-100mg/day or 0.5 -1.0 mg/kg/day. Acitretin doses were 10-75 mg/day or 1 mg/kg/day

The duration of treatment ranged from 8-16 weeks for trials for induction of remission. One study (Lassus 1987) addressed both induction and maintenance of remission, reporting results at two and six months.

8.2.2. RCTs of retinoids to maintain remission

Two trials were concerned with maintenance of remission of psoriasis. Dubertret and colleagues (Dubertret 1985) selected patients with "widespread psoriasis" affecting at least 40% body surface area and gave "clearance treatment" which comprised etretinate 1mg/kg/day in combination with PUVA, three times per week. Providing 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 was half the highest dose tolerated during clearance treatment. Both groups received PUVA treatment once a week for the first two months of the maintenance treatment phase.
Lassus and colleagues (Lassus 1987) enrolled patients with "long-standing, severe psoriasis" into their study. They compared three different doses of acitretin with placebo for both 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.

8.3. Comparative efficacy of retinoids

8.3.1. RCTs comparing retinoids with placebo

Nine trials compared either etretinate or acitretin with placebo. Results were extractable from six of these trials, giving 11 patient series involving a total of 310 participants. Table 8.9 shows the outcome criteria and response rates and figure 8.2 shows the odds ratios for the 11 patient series and the pooled value. In spite of the factors mentioned above, heterogeneity was not demonstrated and so a fixed effects model was used to obtain the pooled effect size (OR = 5.02, 95% CI 2.97 –

8.49). It should be noted that three of the trial protocols (Lassus 1980, Lassus 1987, Melis 1984) permitted the use of topical steroids, which, in theory, would contribute further to heterogeneity in the results.

8.3.1.1. Sensitivity analysis

The effect size for retinoids versus placebo was calculated by different methods for all doses of retinoids and then for doses above 50 mg/day. (Fixed effects models were used for RR and OR; the random effects model was applied to the RD because the data were heterogeneous.) The results are shown in Table 8.10. The conclusion that retinoids are superior to placebo is is not altered by the method of analysis and is therefore robust. However, the removal of the lower dose series clearly increases effect size, for example the rate difference increases from 0.27 (95% CI 0.09 – 0.45) to 0.37 (95% CI 0.13 – 0.61). Figure 8.3 shows the corresponding forest plot for the OR. It can therefore be concluded that the effect size is sensitive to changes in dose.

8.3.2. RCTs comparing acitretin with etretinate

Five trials compared acitretin with etretinate. Results were extractable from four of these trials. Four patient series, involving a total of 419 participants, compared equal doses of acitretin and etretinate. Table 8.11 shows the outcome criteria and response rates and figure 8.4 shows the odds ratios and the pooled value (OR = 1.00, 95% CI 0.64 - 1.57) for these four series. The 95% confidence interval for each of the individual results includes the value of zero, the data are statistically homogeneous and the pooled value, as expected, falls on the 'line of no difference'. This suggests that etretinate and acitretin were equally efficacious in inducing remission of psoriasis.

8.3.3. RCTs comparing retinoid-PUVA combinations with other treatments

Seven trials compared acitretin or etretinate in combination with PUVA against PUVA alone (with or without placebo tablets). Results were extractable from five of these trials, involving a total of 283 participants. Table 8.12 and figure 8.5 show the odds ratios for six patient series from seven trials for which results were available in a suitable form. Table 8.13 shows the corresponding mean differences in number of PUVA treatments (insufficient data were available to compare mean differences in time to clearance or total PUVA doses). Two trials (Parker 1984, Sommerburg 1993) very nearly demonstrated a positive odds ratio for RePUVA versus PUVA (see table 8.12, figure 8.5). The data were statistically homogeneous and the pooled value shows a small positive effect for RePUVA treatment. The corresponding data for PUVA exposure were reported differently in

the different studies (e.g. reduction in total PUVA dose or reduction in "time to clearance") and so it was not possible to demonstrate a consistent reduction in PUVA exposure. Table 8.13 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 variability.

8.3.4. RCTs comparing etretinate with cyclosporin

Table 8.14 and Figure 8.6 show the success rates for two patient series from two RCTs involving 286 participants. These were both large studies and the results clearly show that etretinate was less efficacious in inducing remission of psoriasis than was cyclosporin (odd ratios were 0.08, 95% CI 0.01 – 0.62 (Finzi 1993) and 0.11, 95% CI 0.05 –0.24 (Mahrle1995)). Nevertheless it should be noted that the response rate to etretinate in the study by Finzi and colleagues (Finzi 1993) was 0.73 (29/40), which, in itself is a very satisfactory response rate. This study used a daily etretinate dose of 0.75 mg/kg whereas in the study by Mahrle and colleagues (Mahrle 1995) a dose of 0.5 mg/kg was used. These trials have been described previously in section 7.3.1. The pooled odds ratio for cyclosporin versus etretinate was 9.34 (95% CI 4.69 – 8.62) and the reciprocal of this figure gives the odds ratio for etretinate versus cyclosporin, 0.11 (0.05 – 0.21). As both the point estimate and the limits of the 95% confidence interval are less than one, etretinate is clearly shown to be less effective than cyclosporin.

8.3.5. RCTs comparing retinoid-UVB (broad-band and narrow-band) combinations with other treatments

Table 8.15 shows the response rates in five patient series from four trials for which results were available in a suitable form. Three series compared a retinoid-UVB (or retinoid NBUVB) combination with UVB alone (Green 1992, Ruzicka 1990, Iest 1989). On each occasion the combination appeared to be superior to phototherapy alone (pooled OR 4.48, 95% CI 1.95 – 10.27) (see figure 8.7). In addition, Iest and Boer (Iest 1989) compared the combination of acitretin and UVB with acitretin alone, and again, the combination was superior to the single treatment (OR 28, 95% CI 2.07 – 379). Green and colleagues (Green 1992) also compared a retinoid-NBUVB combination with a retinoid and PUVA combination and reported no difference in success rates.

8.3.6 RCTs comparing retinoid-topical treatment combinations with other treatment s

Table 8.16 shows the success rates differences for six patient series from four trials. Three series compared a combination of retinoid and topical steroid with a topical steroid (and placebo) (Binazzi 1981, Christiansen 1982b, van der Rhee 1980b). The results showed that the combination was more effective than topical corticosteroids alone (pooled OR 2.63, 95% CI 1.45 – 4.77) (see figure 8.8). Two series compared the combination with systemic retinoid and placebo cream or ointment (Christiansen 1982a, van der Rhee 1980a). Again, the combinations were superior to retinoid alone (pooled OR 2.98, 95% CI 1.53 – 5.81).

One series compared the combination of acitretin and calcipotriol with acitretin and placebo ointment (van de Kerkhof 1998). Once again, the combination was superior to the single treatment (OR 2.98, 95% CI 1.47- 6.03).

8.3.7 RCTs of retinoids to maintain remission

Two trials, involving 116 participants, examined the effects of retinoids in maintaining remission. Dubertret and colleagues (Dubertret 1985) compared etretinate with placebo over a 12 month period. Both groups also received PUVA for the first two months. They reported that relapses occurred more frequently in the placebo-treated group than in the etretinate treated group. Lassus and colleagues (Lassus 1987) compared acitretin at three different dose levels with placebo. After six months' treatment there were no significant differences between the four groups. The authors pointed out that the final evaluation was carried out in the summer when many patients experience "at least partial spontaneous remission", however, patients in all groups were also allowed to use steroid ointment as required.

8.4 Side effects of oral retinoids

Side effects were reported in a number of different ways (e.g. percentage of patient-weeks when specific side effects were reported, percentage of patients reporting side effects etc) which makes it difficult to make direct comparisons between trials. Most authors commented that skin and mucous membrane effects were common amongst patients receiving retinoids but there was no consistent reporting of drop-outs due to side-effects.

8.5 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, in part be explained by the small numbers in the study by Goldfarb (Goldfarb 1988). A suggestion of a dose response relationship is discernible with doses below 75mg/day or 1mg/kg/day generally performing no better than placebo. However, the effects of concurrent topical steroid treatment (Lassus 1980, Melis 1984 and Lassus 1987) could have improved the responses in the placebo-treated groups. Furthermore, the mix of patients (by psoriasis type) could also have influenced the results as some participants with palmo-plantar pustular psoriasis were included in some trials. This condition is more difficult to treat and the inclusion of these participants may therefore have reduced the apparent effectiveness of the retinoid treatment.

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 to achieve a satisfactory response. The combination of a retinoid with UVB or, more recently, narrow-band 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 studies concerned (Iest 1989 and Ruzicka 1990) achieved positive results using low doses of retinoid (30 or 35 mg/day of acitretin). Only one study compared the retinoid plus NBUVB combination with rePUVA and reported no differences in efficacy (Green 1992). This 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.

When compared with cyclosporin, etretinate appeared to be relatively ineffective, but the individual response rates tell a different story. In one study (Finzi 1993) etretinate was given at a dose of 0.75 mg/kg/day resulting in a success rate of 73%, which is better than the success rate achieved in all of the placebo-controlled trials. In the other trial (Mahrle 1995) a dose of 0.5 mg/kg/day was given and the success rate was only 16%, which lends further support to the view that doses of less than 0.75mg/kg/day are not effective.

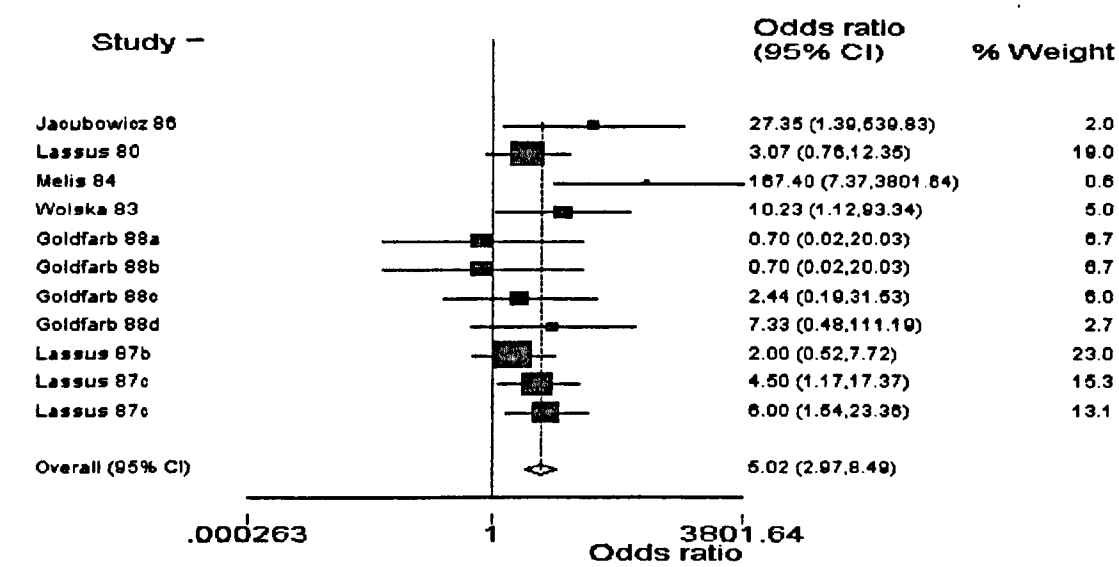
Trials of combinations of systemic retinoids with topical treatments involved either steroids (three trials) or calcipotriol (one trial). These trials generally had larger numbers of participants than the other trials in this review and the results suggested a clear trend in favour of the combinations. However, it should be noted that the endpoints of these trials were subjective for the most part.

8.6 Conclusions

Acitretin is as effective as etretinate in the treatment of chronic plaque psoriasis, however, systemic retinoids (acitretin and etretinate) are only modestly effective as a monotherapy for severe psoriasis. Mucocutaneous side-effects (such as dry mucous membranes and peeling skin around the lips and nose) occur in the majority of patients and other risks such as hyperlipidaemia and teratogenicity must be borne in mind.

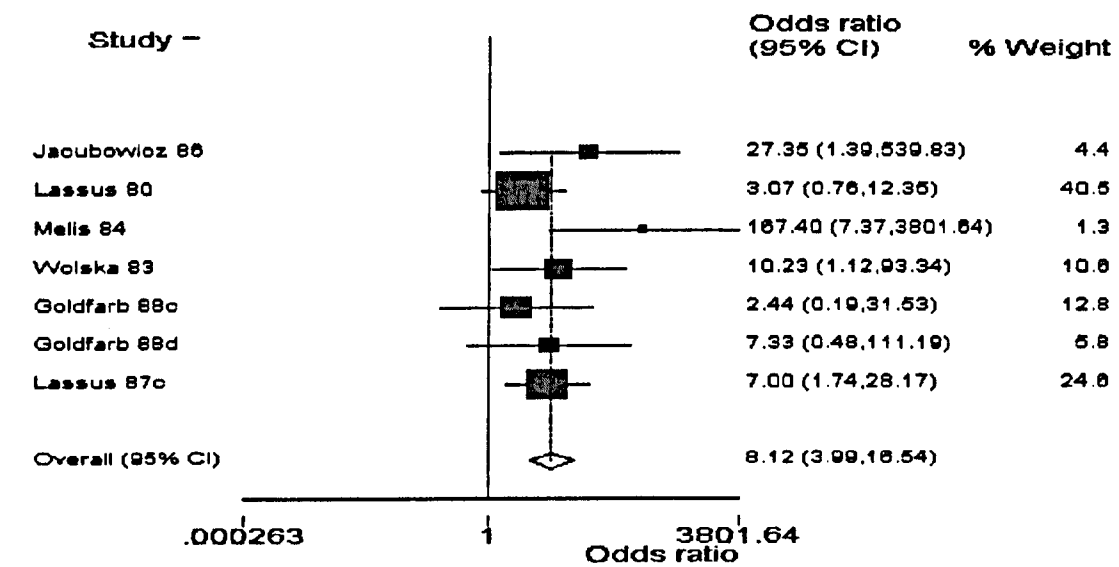
Combination treatments, using a retinoid plus PUVA or a retinoid plus UVB/NBUVB offer ways of obtaining the benefits of both treatments with a lower dose of one of the treatments. Combinations with topical corticosteroids are also more effective than either treatment alone.

Figure 8.2: Forest plot showing odds ratios of trials of retinoids (all doses) vs. placebo.



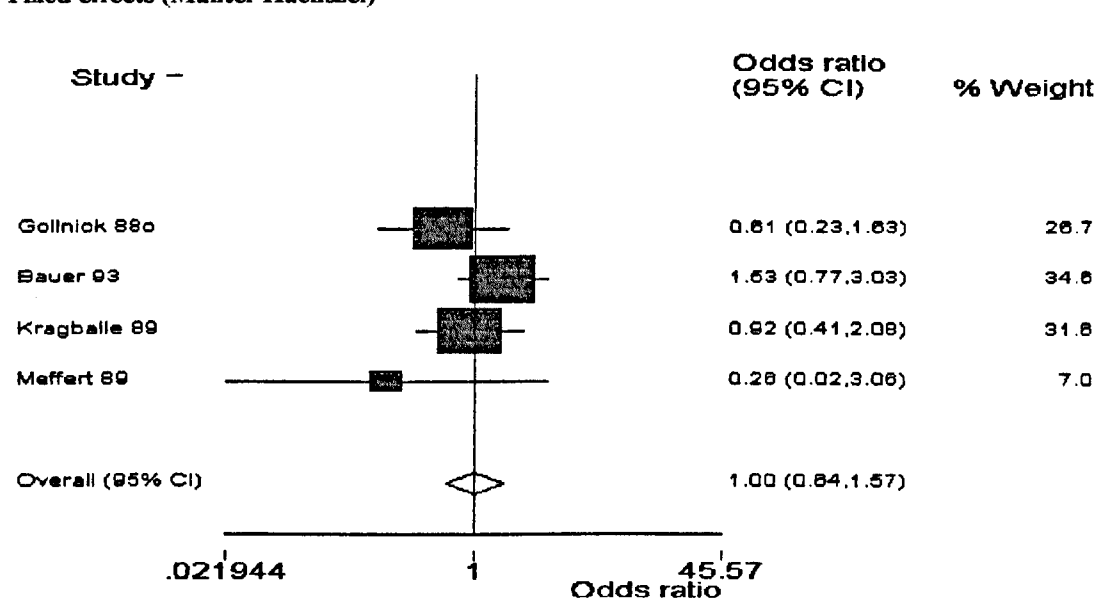
Heterogeneity chi-squared = 11.88 (d.f. = 10) p = 0.293; Test of OR=1 : z= 6.03 p = 0.000

Figure 8.3: Forest plot showing odds ratios of trials of retinoids (doses of 50mg/day and above) vs. placebo.



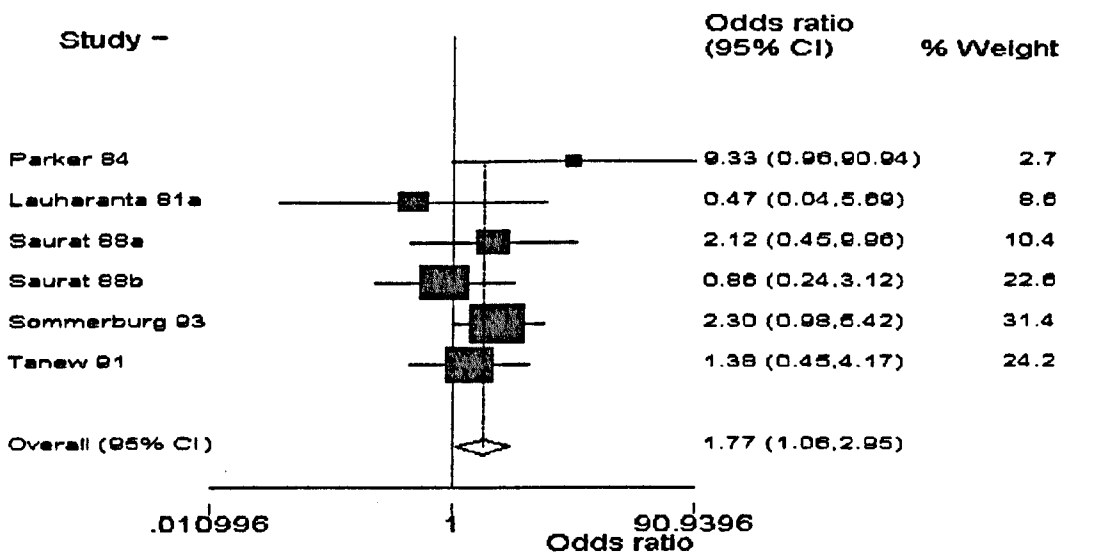
Heterogeneity chi-squared = 7.06 (d.f. = 6) p = 0.315; Test of OR=1 : z= 5.77 p = 0.000
without placebo.

Figure 8.4: Forest plot showing odds ratios of trials comparing acitretin (doses of 30mg/day or above) with etretinate.



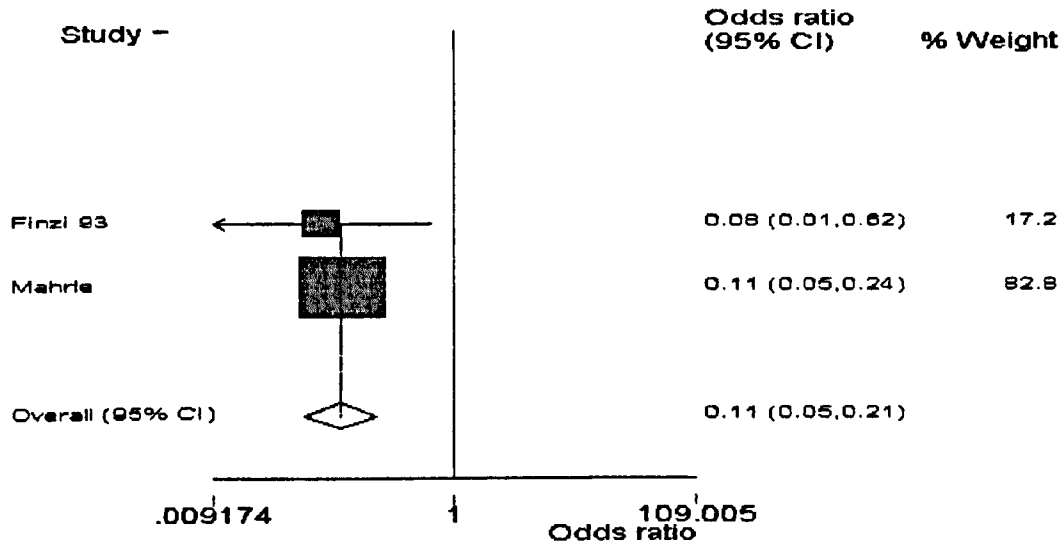
Heterogeneity chi-squared = 3.65 (d.f. = 3) p = 0.302; Test of OR=1 : z= 0.01 p = 0.992

Figure 8.5: Forest plot showing odds ratios of trials comparing RePUVA with PUVA with or without placebo.



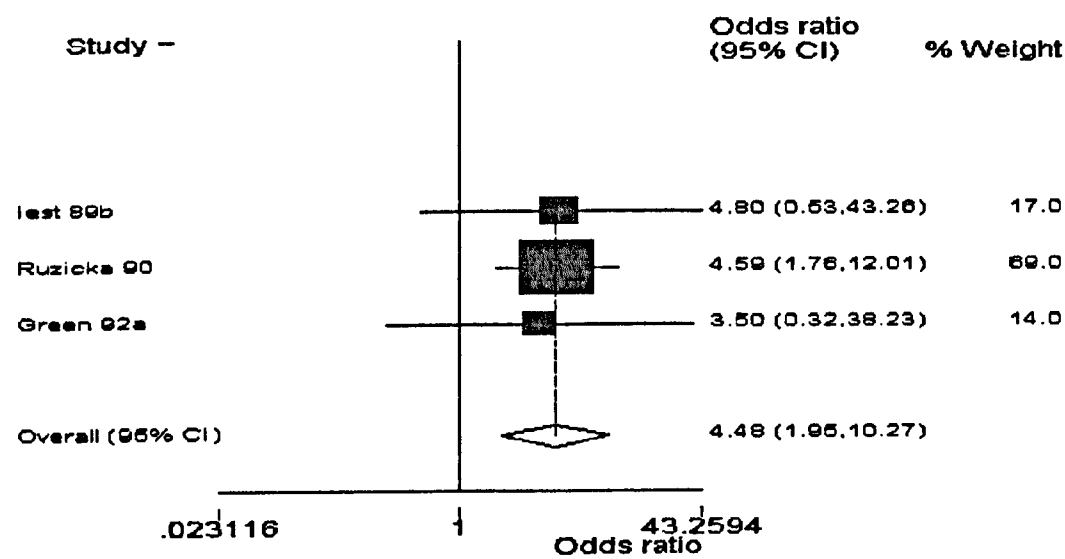
Heterogeneity chi-squared = 4.95 (d.f. = 5) p = 0.422; Test of OR=1 : z= 2.17 p = 0.030

Figure 8.6: Forest plot showing odds ratios of trials comparing etretinate with cyclosporin
Fixed effects (Mantel-Haenszel)



Heterogeneity chi-squared = 0.13 (d.f. = 1) p = 0.716; Test of OR=1 : z= 6.35 p = 0.000

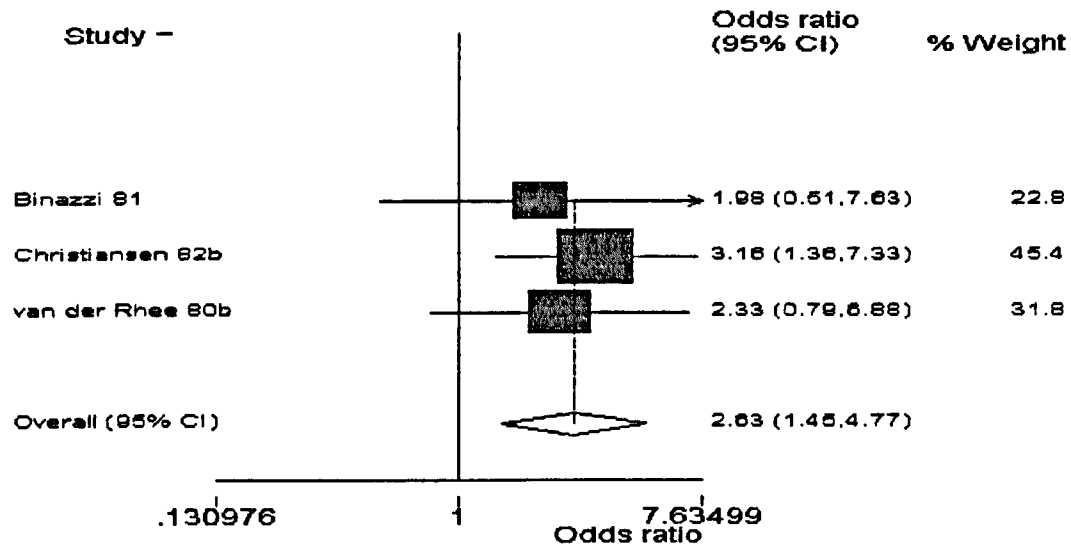
Figure 8.7: Forest plot showing odds ratios of trials comparing ReUVB with UVB alone
Fixed effects (Mantel-Haenszel)



Heterogeneity chi-squared = 0.05 (d.f. = 2) p = 0.977; Test of OR=1 : z= 3.54 p = 0.000

Figure 8.8: Forest plot showing odds ratios of trials comparing retinoid-steroid combinations with topical steroids alone.

Fixed effects (Mantel-Haenszel)



Heterogeneity chi-squared = 0.40 (d.f. = 2) p = 0.820; Test of OR=1 : z= 3.18 p = 0.001

Table 8.2: Design of trials comparing retinoids (acitretin (ACI) or etretinate (ETR)) with placebo

Reference	Intervention (daily dose)	Comparator	Design & duration	Numbers (active:PLO)	Inclusion criterion (disease severity)	Success criterion
Induction of remission of psoriasis						
Jakubowicz 86	ETR 1mg/kg	PLO	DB, PG, 16 wks	15:15	Not reported	almost/complete remission
Lassus 80	ETR 50 mg	PLO	DB, Xover, 52wks	48:49	"Psoriasis of long duration"	complete remission
Melis 84	ETR 1 mg/kg	PLO	DB, PG, 10 wks	15:15	>5% BSA	marked improvement or complete remission
Wolska 83	ETR 1 mg/kg	PLO	DB, PG, 16 wks	20:20	"severe psoriasis"	almost or complete clearing
Goldfarb 88a	ACI 10mg	PLO	DB, PG, 8 wks	5: 12	>10% BSA	≥ 75% improvement in global score
Goldfarb 88b	ACI 25 mg	PLO	DB, PG, 8 wks	5:12	>10% BSA	≥ 75% improvement in global score
Goldfarb 88c	ACI 50mg	PLO	DB, PG, 8 wks	11:12	>10% BSA	≥ 75% improvement in global score
Goldfarb 88d	ACI 75mg	PLO	DB, PG, 8 wks	5:12	>10% BSA	≥ 75% improvement in global score

Table 8.2 continued

Reference	Intervention (daily dose)	Comparator	Design & duration	Numbers (active:PLO)	Inclusion criterion (disease severity)	Success criterion
Kingston 87a	ACI 10mg,	PLO	DB, PG, 8 wks	5:6	>20% BSA	≥ 75% clearing of psoriatic plaques
Kingston 87b	ACI 50mg	PLO	DB, PG, 8 wks	5:6	>20% BSA	≥ 75% clearing of psoriatic plaques
Kingston 87c	ACI 75mg	PLO	DB, PG, 8 wks	5:6	>20% BSA	≥ 75% clearing of psoriatic plaques
Lassus 87a	ACI 10mg,	PLO	DB, PG, 8 wks	20:20	"long-standing severe psoriasis"	≥ 75% decrease in PASI or PASI <8
Lassus 87b	ACI 25mg	PLO	DB, PG, 8 wks	20:20	"long-standing severe psoriasis"	≥ 75% decrease in PASI or PASI <8
Lassus 87c	ACI 50mg	PLO	DB, PG, 8 wks	20:20	"long-standing severe psoriasis"	≥ 75% decrease in PASI or PASI <8
Madhok 87a	ACI 25mg	PLO	DB, PG, 8 wks	2:3	>15% BSA	Not reported for DB phase of study
Madhok 87a[7]	ACI 50mg	PLO	DB, PG, 8 wks	3:3	>15% BSA	Not reported for DB phase of study
Olsen 89a	ACI 25mg	PLO	DB, PG, 8 wks	4:5	>10% BSA	Not reported
Olsen 89b	ACI 50 mg	PLO	DB, PG, 8 wks	6:5	>10% BSA	Not reported

Table 8.2 continued

Reference	Intervention (daily dose)	Comparator	Design & duration	Numbers (active:PLO)	Inclusion criterion (disease severity)	Success criterion
Maintenance of remission of psoriasis						
Dubertret 85	ETR	PLO	DB, PG, 52 wks	16:20	Psoriasis cleared (<10% initial global clinical score) by ETR 1mg/kg/d + PUVA 3 times per week	Absence of relapse (= clinical score >50% initial score)
Lassus 87d	ACI 10mg,	PLO	DB, PG, 26 wks	20:20	"long-standing severe psoriasis"	not reported
Lassus 87e	ACI 25mg	PLO	DB, PG, 26 wks	20:20	"long-standing severe psoriasis"	not reported
Lassus 87f	ACI 50mg	PLO	DB, PG, 26 wks		"long-standing severe psoriasis"	not reported

Key: PSI Psoriasis severity index

Notes:

Lassus 80 Patients received 100 mg /day for the first two weeks and then a maintenance dose of 50 mg/day. Double blind, pre cross-over 13 week phase used for analysis

Lassus 87 Study covered both induction a and maintenance of remission. Initial 8 week phase - results for induction of remission. Maintenance treatment assessed at 26 weeks. Authors comment that "after 6 months the difference in efficacy between placebo and the different doses of etretin (acitretin) was no longer significant".

Table 8.3: Design of trials comparing acitretin with etretinate

Reference	Intervention (daily dose)	Comparator	Design & duration	Numbers (ACI:ETR)	Inclusion criterion (disease severity)	Success criterion
Gollnick 88a	ACI 10mg	ETR 50mg/d	DB, PG, 8 wks	46:43	>20% BSA	≥ 75% decrease in PASI (or PSI[a])
Gollnick 88b	ACI 25mg	ETR 50mg/d	DB, PG, 8 wks	43:43	>20% BSA	≥ 75% decrease in PASI (or PSI[a])
Gollnick 88c	ACI 50mg	ETR 50mg/d	DB, PG, 8 wks	43:43	>20% BSA	≥ 75% decrease in PASI (or PSI[a])
Bauer 93	ACI 50mg	ETR 50mg/d	DB, PG, 12 wks	71:74	"severe psoriasis"	≥ 75% decrease in PSI[b]
Gollnick 93	ACI 50mg	ETR 50mg/d	DB, PG, 24 wks	71:74		
Kragballe 89	ACI 40mg	ETR 40mg/d	DB, PG, 12 wks	127:41	"long-standing severe psoriasis"	marked or total clearance
Ledo 88	ACI 30mg	ETR 30mg/d	DB, PG, 12 wks	10:10	"severe psoriasis"	not reported
Meffert 89	ACI 30mg	ETR 30mg/d	DB, PG, 12 wks	10:10	"severe psoriasis"	marked improvement or remission

Key to table 8.3:

PSI* (0-36)	"Corrected PASI" - range 0-36
PSI (0-48)	Psoriasis severity index - sum of the intensity of erythema, infiltration and scaling on head, trunk, arms & legs, 0-4 scale for each

Notes

Gollnick 93	This study is a follow-up study of the patients in Bauer 93

Table 8.4: Design of trials comparing of retinoids (ACI or ETR) – PUVA combinations [RePUVA] with other treatments

Reference	Intervention	Comparator(s)	Design & duration	Numbers (Test:comparator)	Inclusion criterion (disease severity)	Success criterion
Parker 84	ETR 0.75mg/kg + PUVA	PUVA + PLO	NB, PG, 10 wks	15:13	>20% BSA	clearance (≡ less than 2% BSA affected)
Lauharanta 81a	ETR 60mg/d 4 wks then ETR + PUVA 6 wks	PUVA	NB, PG, 10	20:20	"severe psoriasis"	≥ 75% decrease in PASI
Lauharanta 81b	ETR 60mg/d 4 wks then ETR + PUVA 6 wks	ETR 60mg/d,	NB, PG, 10	20:20	"severe psoriasis"	≥ 75% decrease in PASI
Lauharanta 81c	ETR 60mg/d 4 wks then ETR + PUVA 6 wks	ETR 60mg/d 4 wks then PUVA 6 wks	NB, PG, 10	20:20	"severe psoriasis"	≥ 75% decrease in PASI
Green 92a	ETR 1mg/kg + PUVA	ETR + NBUVB	NB, PG, variable duration	15:15	"extensive chronic plaque or guttate psoriasis	"satisfactory response"
Green 92b	ETR 1mg/kg + PUVA	NBUVB	ETR 1mg/kg + PUVA	15:15	"extensive chronic plaque or guttate psoriasis	"satisfactory response"
Lauharanta 89	ACI 40mg/d + bath PUVA	ETR 40mg/d + bath PUVA	DB, PG, 10wks	17:17	"widespread plaque-type psoriasis"	≥ 90% decrease in PASI

Table 8.4 continued

Reference	Intervention	Comparator(s)	Design & duration	Numbers (Test:comparator)	Inclusion criterion (disease severity)	Success criterion
Saurat 88a	ACI 50mg/d + PUVA	ETR 50mg/d + PUVA,	DB, PG, 12wks	20:23	severe psoriasis with >20% BSA or erythrodermic psoriasis	≥ 75% decrease in PASI
Saurat 88b	ACI 50mg/d + PUVA	PUVA +PLO	DB, PG, *?duration*	20:22	severe psoriasis with >20% BSA or erythrodermic psoriasis	≥ 75% decrease in PASI
Sommerburg 93	ACI 50mg/d + PUVA	PUVA + PLO	DB. PG	40:43	"generalized chronique plaque psoriasis severe enough to require PUVA"	≥ 75% decrease in PSI (Psoriasis severity index; scale 0-36)
Tanew 91	ACI 1mg/kg + PUVA	PUVA + PLO	DB. PG, 11 wks	30:30	"severe and extensive psoriasis - >20% BSA"	≥ 90% clearance of psoriasis
Maintenance of remission of psoriasis						
Dubertret 85	ETR 0.5 mg + PUVA once a week for 2/12	PLO + PUVA once a week for 2/12	DB, PG, 52 wks	16:20	Psoriasis cleared (<10% initial global clinical score) by ETR 1mg/kg/d + PUVA 3 times per week	Absence of relapse (= clinical score >50% initial score)

Table 8.5: Design of trials comparing retinoid (ACI or ETR) – UVB (broad-band or narrow-band) with other treatments

Reference	Intervention	Comparator(s)	Design & duration	Numbers (Test:comparator)	Inclusion criterion (disease severity)	Success criterion
Green 92a	ETR 1mg/kg + NBUVB	NBUVB,		15:15	"extensive chronic plaque or guttate psoriasis	"satisfactory response"
Green 92b	ETR 1mg/kg + NBUVB	ETR 1mg/kg + PUVA	NB, PG, variable duration	15:15	"extensive chronic plaque or guttate psoriasis	"satisfactory response"
Iest 89	ACI + UVB	ACI	NR,PG, L/R 30 exposures	9:9	chronic plaque psoriasis ; ≥ 10% BSA	≥ 80% clearance
Iest 89	ACI + UVB	UVB	NR, PG 30 exposures	9:32	chronic plaque psoriasis ; ≥ 10% BSA	≥ 80% clearance
Lowe 91	ACI 50mg/d + UVB	UVB + PLO	NB, PG, 12 wks	16:18	moderate-severe psoriasis; >20% BSA	not reported
Ruzicka 90	ACI 35mg/d + UVB	UVB + PLO	DB, PG, 8 wks	40:38	generalised chronic plaque or "exanthematous" type psoriasis severe enough to require combination treatment	≥ 75% decrease in PASI

Table 8.6: Design of trials comparing retinoid (ACI or ETR) – topical treatment combinations with other treatments

Reference	Intervention	Comparator(s)	Design & duration	Numbers (Test:comparator)	Inclusion criterion (disease severity)	Success criterion
Retinoids combined with steroids						
Binazzi 81	ETR +difluocortolone valerate 0.1% oint.	difluocortolone valerate 0.1% oint.+ PLO	DB, PG, variable	30:30	not reported ("patients with psoriasis")	≥ 75% decrease in total score (scale 0-16)
Christiansen 82a	ETR 1mg/kg + betamethasone valerate 0.1% cream	ETR + PLO cream	DB, PG, 8 wks	50:50	"patients with psoriasis vulgaris"	complete or satisfactory remission
Christiansen 82b	ETR 1mg/kg + betamethasone valerate 0.1% cream	betamethasone valerate 0.1% cream + PLO	DB, PG, 8 wks	50:46	"patients with psoriasis vulgaris"	complete or satisfactory remission
van der Rhee 80	ETR 0.66 mg/kg + triamcinolone acetonide 0.1% & salicylic acid cream	ETR + PLO cream	DB, PG, 6 wks	30:30	>15%BSA	overall improvement
van der Rhee 80	ETR 0.66 mg/kg + triamcinolone acetonide 0.1% & salicylic acid cream	triamcinolone acetonide 0.1% & salicylic acid cream + PLO	DB, PG, 6 wks	30:30	>15%BSA	overall improvement

Table 8.6 continued

Reference	Intervention	Comparator(s)	Design & duration	Numbers (Test:comparator)	Inclusion criterion (disease severity)	Success criterion
Retinoid with calcipotriol						
van de Kerkhof 98	ACI 20mg/d+ calciptriol	ACI 20mg/d + PLO cream	DB, PG, 12 wks	76:59	"severe or extensive psoriasis vulgaris ...not responsive to topical treatment alone"	clearance or marked improvement

Table 8.7: Design of trials of etretinate (ETR) versus cyclosporin

Reference	Intervention	Comparator	Design & duration	Numbers (ETR:CSA)	Inclusion criterion (disease severity)	Success criterion
Finzi 93	ETR 0.75 mg/kg	CSA 5.0mg/kg	DB, PG, 12 wks	36:40	PASI > 15	≥ 75% decrease in PASI or PASI < 8
Mahrle 95	ETR 0.5 mg/kg	CSA 2.5 mg/kg	SB, PG, 10 wks	70:140	"moderate-severe"	≥ 70% decrease in PASI

Table 8.8: Trial of different dosage schedules for acitretin

Reference	Intervention	Comparator	Design & duration	Numbers (test:comparator)	Inclusion criterion (disease severity)	Success criterion
Berbis 89	ACI increasing dose	ACI constant dose	DB, PG, 6 wks	22:27	not reported ("patients with psoriasis")	not reported
Berbis 89	ACI increasing dose	ACI decreasing dose	DB, PG, 6 wks	22:25	not reported ("patients with psoriasis")	not reported

Table 8.9: Success criteria, response rates and effects size: Trials comparing retinoids (ACI or ETR) with placebo

Reference	Intervention (daily dose)	Comparator	Numbers (active:PLO)	Success criterion	Response rates	Effect size OR (95% CI)
Induction of remission of psoriasis						
Jakubowicz 86	ETR 1mg/kg	PLO	15:15	almost/complete remission	7/15:0/15	27.35 (1.39 – 539)
Lassus 80	ETR 100 mg/d	PLO	48:49	complete remission	8/48:3/49	3.07 (0.76 – 12.35)
Melis 84	ETR 1 mg/kg	PLO	15:15	marked improvement or complete remission	13/15:0/15	167 (7.37 – 3801)
Wolska 83	ETR 1 mg/kg	PLO	20:20	almost or complete clearing	7/20:1/20	10.23 (1.12 – 93.34)
Goldfarb 88a	ACI 10mg, 25mg 50mg or 75mg/d	PLO	5:12	≥ 75% improvement in global score	0/5:1/12	0.70 (0.02 – 20.03)
Goldfarb 88b	ACI 25 mg	PLO	5:12	≥ 75% improvement in global score	0/5: 1/12	0.70 (0.02 – 20.03)
Goldfarb 88c	ACI 50mg	PLO	11:12	≥ 75% improvement in global score	2/11: 1/12	2.44 (0.19 – 31.53)
Goldfarb 88d	ACI 75mg	PLO	5:12	≥ 75% improvement in global score	2/5: 1/12	7.33 (0.48 – 111.19)
Kingston 87a	ACI 10mg,	PLO	5:6	≥ 75% clearing of psoriatic plaques	not extractable	
Kingston 87b	ACI 50mg	PLO	5:6	≥ 75% clearing of psoriatic plaques	not extractable	
Kingston 87c	ACI 75mg	PLO	5:6	≥ 75% clearing of psoriatic plaques	not extractable	

Table 8.9 continued

Reference	Intervention (daily dose)	Comparator	Numbers (active:PLO)	Success criterion	Response rates	Effect size OR (95% CI)
Lassus 87a	ACI 10mg,	PLO	20:20	≥ 75% decrease in PASI or PASi <8	8/20:5/20	2.00 (0.52 – 7.72)
Lassus 87b	ACI 25mg	PLO	20:20	≥ 75% decrease in PASI or PASi <8	12/20:5/20	4.50 (1.17 – 17.37)
Lassus 87c	ACI 50mg	PLO		≥ 75% decrease in PASI or PASi <8	14/20:5/20	6.00 (1.54 – 23.36)
Madhok 87	ACI 25mg or 50 mg/d	PLO	2:3 3:	Not reported for DB phase of study	not extractable	
Olsen 89	ACI 25mg or 50 mg/d	PLO	4:5 6:	Not reported	not extractable	

Table 8.10 : Comparison of effects sizes for trials of retinoids vs. placebo by effect measure and dose

Effect measure	**Effect size – All doses (95% CI)**	**Effect size – Doses > 50mg/day (95% CI)**
Risk ratio (RR) (M-H fixed)	3.23 (2.15 – 4.86)	4.78 (2.69 – 8.50)
Odds ratio (OR) (M-H fixed)	5.02 (2.97 – 8.49)	8.12 (3.99 – 16.54)
Risk difference (RD) (D&L random)	0.27 (0.09 –0.45)	0.37 (0.13 – 0.61)

Table 8.11: Success criteria and response rates: Trials comparing acitretin with etretinate

Reference	Intervention	Comparator	Numbers (ACI:ETR)	Success criterion	Response rates
Gollnick 88a	ACI 10mg	ETR 50mg/d	46:43	≥ 75% decrease in PASI (or PSI[a])	9/46:13/43
Gollnick 88b	ACI 25mg	ETR 50mg/d	43:43	≥ 75% decrease in PASI (or PSI[a])	8/43:13/43
Gollnick 88c	ACI 50mg	ETR 50mg/d	43:43	≥ 75% decrease in PASI (or PSI[a])	9/43/13/43
Bauer 93	ACI 50mg/d	ETR 50mg/d	71:74	≥ 75% decrease in PSI[b]	29/71:23/74
Gollnick 93	ACI 50mg/d	ETR 50mg/d	71:74		
Kragballe 89	ACI 40mg/d	ETR 40mg/d	127:41	marked or total clearance	94/127:31/41
Ledo 88	ACI 30mg/d	ETR 30mg/d	10:10	not reported	not extractable
Meffert 89	ACI 30mg/d	ETR 30mg/d	10:10	marked improvement or remission	1/10:3/10

Table 8.12: Success criteria and response rates: Trials comparing retinoids (ACI or ETR) -PUVA combinations [RePUVA] with other treatments

Reference	Intervention	Comparator(s)	Numbers (Test: comparator)	Success criterion	Success rates	Odds ratio (95% CI)
Parker 84	ETR 0.75mg/kg + PUVA	PUVA + PLO	15:13	clearance (≡ less than 2% BSA affected)	14/15:9/15	9.33 (0.96 – 90.94)
Lauharanta 81a	ETR 60mg/d 4 wks then ETR + PUVA 6 wks	PUVA	20:20	≥ 75% decrease in PASI	18/20:19/20	0.47 (0.04 – 5.69)
Lauharanta 81b	ETR 60mg/d 4 wks then ETR + PUVA 6 wks	ETR 60mg/d,	20:20	≥ 75% decrease in PASI	18/20:13/20	4.85 (0.86 –27.22)
Lauharanta 81c	ETR 60mg/d 4 wks then ETR + PUVA 6 wks	ETR 60mg/d 4 wks then PUVA 6 wks	20:20	≥ 75% decrease in PASI	18/20:17/20	1.5 (0.24 – 10.70)
Green 92a	ETR 1mg/kg + PUVA	ETR + NBUVB	15:15	"satisfactory response"	15/15:14/15	3.21 (0.12 – 85.21)
Green 92b	ETR 1mg/kg + PUVA	NBUVB	15:15	"satisfactory response"	15/15:12/15	8.68 (0.41 – 184.28)
Lauharanta 89	ACI 40mg/d + bath PUVA	ETR 40mg/d + bath PUVA	17:17	≥ 90% decrease in PASI	17/17:17/17	1.0 (0.02 – 53.28

Table 8.12 continued

Reference	Intervention	Comparator(s)	Numbers (Test: comparator)	Success criterion	Success rates	Odds ratio (95% CI)
Saurat 88a	ACI 50mg/d + PUVA	PUVA +PLO	20:22	≥ 75% decrease in PASI	17/20: 16/22	2.12 (0.45 – 9.96)
Saurat 88b	ETR 50mg/d + PUVA	PUVA +PLO	23:22	≥ 75% decrease in PASI	16/23: 16/22	0.86 (0.24 – 3.12)
Sommerburg 93	ACI 50mg/d + PUVA	PUVA + PLO	40:43	≥ 75% decrease in PSI	28/44:19/44	2.30 (0.98 – 5.42)
Tanew 91 [28]	ACI 1mg/kg + PUVA	PUVA + PLO	30:30	≥ 90% clearance of psoriasis	22/30:20/30	1.38 (0.45 –4.17)
Maintenance of remission of psoriasis						
Dubertret 85 [57]	ETR 0.5 mg + PUVA once a week for 2/12	PLO + PUVA once a week for 2/12	16:20	Absence of relapse (= clinical score >50% initial score)	10/16:5/20	5.0 (1.19 – 20.92)

Table 8.13: Differences in cumulative UVA doses in trials comparing retinoid-PUVA combinations (RePUVA) with PUVA (± placebo)

Author/yr	**Numbers (RePUVA : PUVA)**	**Retinoid**	**Success rates (RePUVA: PUVA)**	**Mean UVA dose in J/cm^2 (RePUVA:PUVA)**	**Difference in mean UVA doses in J/cm^2 (95% CI)** *(RePUVA:PUVA)*
Lauharanta 81a	20/20	Etr	0.80:0.80	66.9 ± 18.7 : 199.5 ± 46.8 sd	132.6 (110.5 – 154.7)
Parker 84	15/15	Etr	0.93:0.60	62.1 ± 9 : 77.3 ± 14.8 se	15.2 (-18.8 – 49.2)
Saurat 88a	23/22	Etr	0.85:0.73	57.8 ± 5.4 : 97.2 ± 12.2 se	39.4 (13.3 – 65.5)
Saurat 88b	20/22	Aci	0.70:0.73	73.7 ± 10.5 : 97.2 ± 12.2 se	23.5 (-8.0 – 55.0)
Tanew 91	30/30	Aci	0.73:0.67	58.7 ± 17.9 : 101.5 ± 15.8 se	42.8 (-4.0 – 89.6)

Key:

sd	standard deviation
se	standard error of the mean
med	median
Aci	acitretin
Etr	etretinate
RePUVA	retinoid + PUVA given together.
NR	not reported

Table 8.14: Success criteria and response rates: Trials comparing etretinate (ETR) with cyclosporin (CSA)

Reference	Intervention	Comparator	Numbers (ETR:CSA)	Success criterion	Response rates	Effect size OR (95% CI)
Finzi 93	ETR 0.75 mg/kg	CSA 5.0mg/kg	36:40	≥ 75% decrease in PASI or PASI < 8	29/40:35/36	0.08 (0.01 –0.62)
Mahrle 95	ETR 0.5 mg/kg	CSA 2.5 mg/kg	70:140	≥ 70% decrease in PASI	11/70:87/140	0.11 (0.05 –0.24)

Table 8.15: Success criteria and response rates: Trials comparing retinoids (ACI or ETR) – UVB (broad-band or narrow-band) combinations

Reference	Intervention	Comparator(s)	Numbers (Test:comparator)	Success criterion	Response rates	Effect size OR (95% CI)
Green 92a	ETR 1mg/kg + NBUVB	NBUVB,	15:15	"satisfactory response"	14/15:12/15	3.5 (0.32 – 38.23)*
Iest 89b	ACI 30 mg/d+ UVB	UVB	9:32	≥ 80% clearance	8/9:20/32	4.80 (0.53 – 43.26)*
Ruzicka 90	ACI 35mg/d + UVB	UVB + PLO	40:38	≥ 75% decrease in PASI	24/42:9/40	4.59 (1.76 – 12.01)*
Lowe 91	ACI 50mg/d + UVB	UVB + PLO	16:18	not reported	not extractable	
Green 92b	ETR 1mg/kg + NBUVB	ETR 1mg/kg + PUVA	15:15	"satisfactory response"	14/15:15/15	0.30 (0.01 – 8.28)
Iest 89a	ACI 30 mg/d + UVB	ACI	9:9	≥ 80% clearance	8/9:2/9	28 (2.07 – 379)

* Pooled value (fixed) 4.48 (95% CI 1.95 – 10.27)

Table 8.16: Success criteria and response rates: Trials of retinoids (ACI or ETR) combined with topical treatment

Reference	Intervention	Comparator(s)	Numbers (Test: comparator)	Success criterion	Response rates	Effect size OR (95% CI)
Retinoids combined with steroids vs steroids + PLO						
Binazzi 81	ETR +difluocortolone valerate 0.1% oint.	difluocortolone valerate 0.1% oint.+ PLO	30:30	≥ 75% decrease in total score (scale 0-16)	7/30:4/30	1.98 (0.51 – 7.63)*
Christiansen 82b	ETR 1mg/kg + betamethasone valerate 0.1% cream	betamethasone valerate 0.1% cream + PLO	50:46	complete or satisfactory remission	29/50:14/46	3.16 (1.36 – 7.33)*
van der Rhee 80b	ETR 0.66 mg/kg + triamcinolone acetonide 0.1% & salicylic acid cream	triamcinolone acetonide 0.1% & salicylic acid cream + PLO	30:30	overall improvement	14/30:10/30	2.33 (0.79 – 6.88)*
Retinoids combined with steroids vs retinoids +PLO						
Christiansen 82a[83]	ETR 1mg/kg + betamethasone valerate 0.1% cream	ETR + PLO cream	50:50	complete or satisfactory remission	29/50:19/50	2.25 (1.10 – 5.02)‡
van der Rhee 80a	ETR 0.66 mg/kg + triamcinolone acetonide 0.1% & salicylic acid cream	ETR + PLO cream	30:30	overall improvement	14/30:4/30	5.69 (1.59 –20-3) ‡
Retinoid with calcipotriol						
van de Kerkhof 98	ACI 20mg/d+ calcipotriol	ACI 20mg/d + PLO cream	76:59	clearance or marked improvement	51/76:24/59	2.98 (1.47 –6.03)

* Pooled value 2.63 (95% CI 1.45 – 4.77) ‡ Pooled value 2.98 (95% CI 1.53 – 5.81)

Chapter 9

Systematic review of trials of oral methotrexate for severe psoriasis

Summary

Methotrexate has been used in the treatment of psoriasis for many years, no eligible RCTs were located for this review. It was therefore not possible to derive estimates of effect size based on the level of evidence demanded by the project protocol.

9.1 Search results

One hundred and eleven citations were identified for methotrexate and psoriasis. Thirty-one citations concerned the therapeutic use of methotrexate for psoriasis. The titles and abstracts were reviewed by two people independently (the author and a consultant dermatologist) to identify possible RCTs. Twenty-nine proved to be case series, retrospective reviews or individual case reports. Two appeared to be reports of RCTs. Both were retrieved and read but failed to fulfil the criteria for inclusion (see Table 9.1). 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.

Figure 9.1 Flow chart to show trials of methotrexate excluded

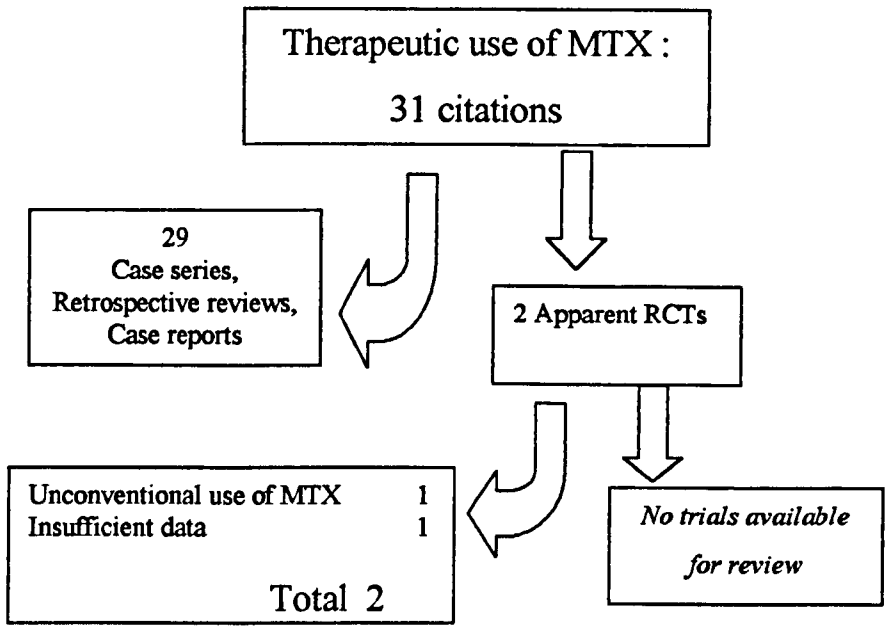


Table 9.1 Methotrexate studies excluded

	First author and year of publication	Reason for Exclusion
1	Liang 1995	Not a RCT of methotrexate in the conventional sense. (Participants were randomised to receive either a large, single intramuscular dose of methotrexate or no injection before receiving a variety of other systemic and topical therapies. Patients included those with all types of psoriasis (guttate, plaque, erythrodermic or pustular))
2	Willkens 1984	Results not extractable: 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

9.2 Discussion

The absence of randomised, controlled trials of methotrexate in the treatment of severe psoriasis is an interesting finding as the drug has had a role in the management of this condition for about thirty years (Said 1997). The results of this study most probably reflect the fact that methotrexate was introduced at a time before the RCT was the standard method for assessing drugs. It is not an expensive drug per se, and by the time its role in psoriasis was recognised and established, its patent had expired and there was no commercial interest in conducting RCTs. Nevertheless, there remains a substantial clinical interest in formal assessment of this drug. This will be necessary in order to determine its effect size relative to other treatments for severe psoriasis and to perform economic evaluations. These would be particularly important as the drug itself is inexpensive but the risk of serious side effects and consequent requirement for rigorous monitoring make the picture more complex than might, at first, be expected.

9.3 Conclusions

On the basis of this systematic review it is not possible to provide an estimate of effect size for methotrexate. This is not to say that no evidence for the effectiveness of methotrexate exists, but that no evidence of the standard required by the protocol, that is, RCTs, could be found.

Chapter 10

Systematic review of trials of phototherapy and photochemotherapy for severe psoriasis

Summary

Fifty eligible RCTs, reporting 55 comparisons were located for this review. The trials are grouped into six broad categories according to the types of comparisons involved: psoralen photochemotherapy treatment schedules; UVB treatment schedules; photochemotherapy versus other phototherapy; phototherapy in combination with retinoids; photochemotherapy using sunlight and phototherapy with topical treatments. There were insufficient similarities between trials to allow pooling of the results. The results are shown as rate differences together with differences in the doses of UV radiation.

10.1 Search Results

Trials of phototherapy and photochemotherapy for psoriasis were identified using the search strategy described in Chapter 6. Three hundred and thirty two citations were identified for psoriasis and PUVA, UVA or UVB. These included studies of the therapeutic use of PUVA, UVA or UVB (RCTs, cohort studies, retrospective studies, case reports & small series) together with reviews and studies of biochemical effects of phototherapy. The titles and abstracts were reviewed by two people independently (the author and a consultant dermatologist) to identify RCTs. Ninety-six records that appeared to be reports of RCTs were retrieved and read. Thirty-six were excluded because they were non-randomised studies (or partially-randomised). Two animal studies were also excluded. A further four studies were excluded because they involved non-randomised, left/right comparisons and four were excluded as the evaluation depended on the response in target lesions only. Non-randomised, left-right comparisons were excluded because this design leaves open the possibility that the investigator could select patients with particular patterns of disease, although, theoretically, only patients with perfectly symmetrical disease would be eligible for such studies. Studies that assessed the response in target lesions only were excluded because this is not an approach that reflects the real-life treatment situation and the results of such studies were not considered comparable with the others included in the review. These 46 reports were excluded from

the final list (See Table 10.1) Thus, 50 RCTs, providing 55 comparisons, were available for inclusion in this review. (See Figure 10.1)

Figure 10.1: Flow chart to show phototherapy and photochemotherapy trials excluded.

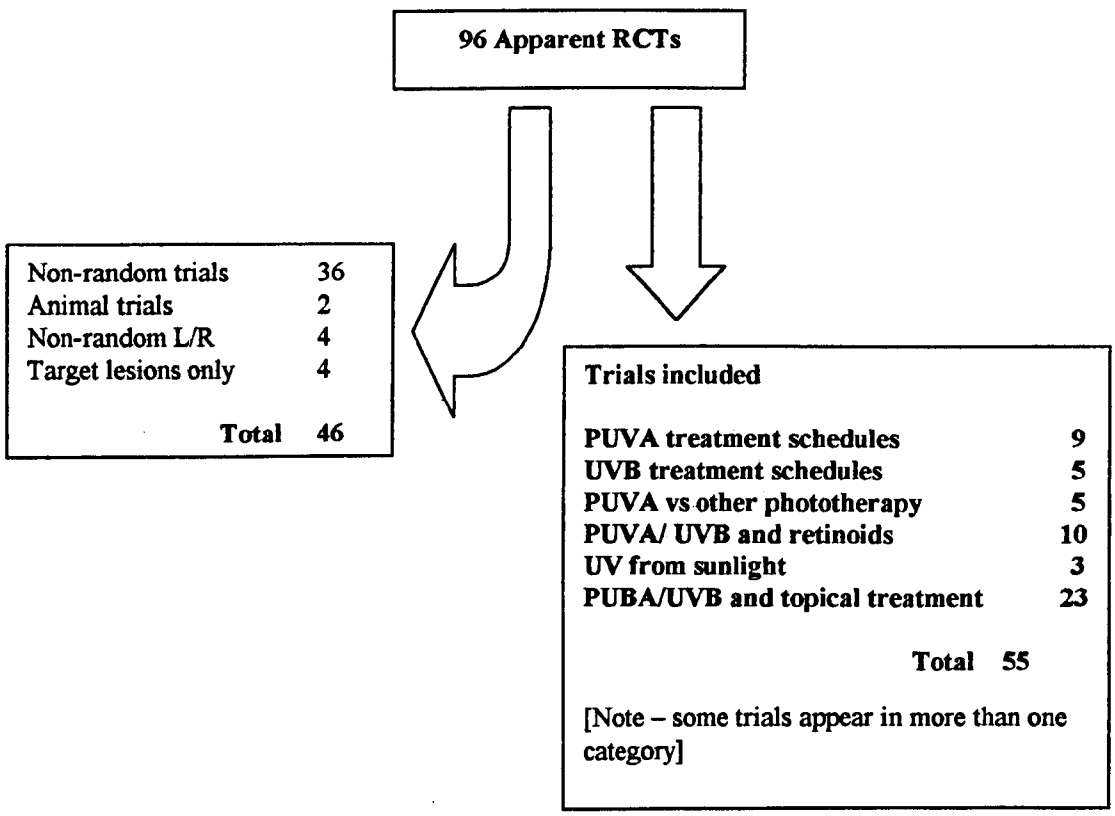


Table 10.1 Studies excluded from phototherapy & photochemotherapy review

	First author and year of publication	Reason for exclusion
1	Bedi, 1979	Non-randomised allocation
2	Berne 1990	Target lesions evaluated
3	Boer 1984	Non-randomised allocation
4	Calzavara Pinton, 1994a	Non-randomised allocation
5	Calzavara Pinton 1994b	Non-randomised allocation
6	Coven 1997	Non-randomised allocation
7	Danno 1983	Non-randomised left/right comparison
8	Darouti, 1988	Non-randomised allocation
9	Diette, 1984	Non-randomised allocation
10	Dubertret, 1979	Animal study, non CT
11	Dubertret, 1979	Animal study, non CT
12	Galosi, A.; Dorn, M., and Przybilla, B. 1985	Non-randomised allocation
13	Eells 1984	Target lesions evaluated
14	Elbracht,1983	Non-randomised allocation
15	Fischer 1977	Non-randomised allocation
16	Fotiades, 1995	Non-randomised allocation
17	George 1993	Non-randomised allocation
18	Gould, 1978	Non-randomised left/right comparison
19	Grupper 1981	Non-randomised allocation
20	Hofmann 1980	Non-randomised allocation
21	Honigsmann 1977	Non-randomised allocation
22	Kar 1994	Non-randomised allocation
23	Karvonen 1989	Non-randomised allocation
24	Kenicer 1981	Non-randomised allocation
25	Kokelj 1996	Non-randomised allocation,
26	Lane Brown 1987	Non-randomised allocation

Table 10.1 continued

	First author and year of publication	Reason for exclusion
27	Langner 1976	Non-randomised allocation
28	Ledo 1981	Non-randomised left/right comparison
29	Lowe 1986	Non-randomised allocation
30	Melski 1977	Partially randomised allocation
31	Momtaz 1984	Non-randomised allocation
32	Nowakowski, 1979	Non-randomised allocation
33	Ortel, 1993	Non-randomised allocation
34	Park, 1985	Non-randomised allocation
35	Paul 1982	Non-randomised allocation
36	Petzelbauer, 1990	Non-randomised allocation
37	Pullmann, 1976	Non-randomised allocation
38	Roenigk 1979	Non-randomised allocation
39	Sonnichsen, 1983	Non-randomised allocation
40	Speight 1994	Non-randomised left/right comparison
41	Swanbeck 1975	Non-randomised allocation
42	Takashima 1988	Target lesions evaluated
43	Talwalkar1981	Non-randomised allocation
44	Wainwright 1998	Target lesions evaluated
45	Wolff 1976	Non-randomised allocation
46	Zhang 1983	Non-randomised allocation

10.2 Description of trials

The characteristics of the trials are summarised in Tables 10.2 –10. 7

These 55 comparisons may conveniently be divided into:

- comparisons of treatment schedules for psoralen photochemotherapy (Table 10.2)
- comparisons of UVB treatment schedules (Table 10.3)
- comparisons of photochemotherapy with other phototherapy treatment schedules (Table 10.4)
- comparisons of phototherapy and retinoids with phototherapy or retinoids (Table 10.5)
- photochemotherapy trials using sunlight as the UV source (Table 10.6)
- comparisons of phototherapy and/or topical treatment schedules (Table 10.7)

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. Twenty-two trials concerned the use of UVA, 21 the use of UVB and five trials involved both UVA and UVB. The remaining three trials used natural sunlight as the UV source.

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 was randomisation stratified by psoriasis type.

Thirteen of the trials used an objective disease severity criterion for inclusion. All of these 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".

Phototherapy regimens were described in detail (dose, frequency and dose adjustments). The duration of treatment was described in weeks or by the number of phototherapy exposures and trial periods varied between two and ten weeks.

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, similar to trials of oral agents. The remainder either did not report a success criterion or relied on descriptions such as "clear", "complete remission", or "satisfactory response". This reflects the established practice with phototherapy and photochemotherapy, where treatment is continued until the skin is clear. The mixture of outcome criteria makes it difficult to compare many of the trials directly.

In addition to the mixture of outcome criteria, 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 are the mix of patients, both in terms of type of psoriasis and skin type, and compliance with treatment.

10.3 Comparative efficacy

10.3.1 RCTs comparing treatment schedules for psoralen photochemotherapy (PUVA):

RCTs involving oral psoralens

Six trials compared different treatment regimens using oral psoralens (Table 10.2).

RCTs comparing psoralen doses

Two trials, involving a total of 162 patients, examined the effects of different psoralen doses for PUVA. Andrew and colleagues (Andrew 1981) showed that 8-methoxypsoralen (8-MOP) at a dose of 40mg was associated with a greater success rate than 8-MOP at a dose of 10mg (RD = 0.72, 95% CI 0.54 - 0.90). Furthermore, a lower mean cumulative UV dose was required to achieve success (54.0 J/cm^2; range 14.5 - 115, compared with 77.0 J/cm^2; range 46-113, respectively). Similarly, Tanew and colleagues (Tanew 1988) showed that 5-methoxypsoralen (5-MOP) cleared psoriasis with a significantly lower mean cumulative UVA dose when given at a dose of 1.2 mg/kg (53 ± 33 J/cm^2) rather than 0.6 mg/kg (132 ± 87 J/cm^2).

RCTs comparing psoralens and psoralen formulations

Liquid versus crystalline psoralen

Lowe and colleagues (Lowe 1987) compared different formulations of the same psoralen in a group of 47 patients. Liquid 8-MOP appeared to be more effective than crystalline 8-MOP, but just failed to show a difference in effect size (RD = 0.25, 95% CI -0.01- 0.51). There was no significant difference in the total energy requirements for the two groups (68.7 J/cm^2 for liquid vs 80.8 J/cm^2 crystalline psoralen).

Oral 8-MOP versus oral 5-MOP

Two studies compared oral 8-MOP with oral 5-MOP. (Berg 1994, Tanew 1988) In the study by Tanew and colleagues (Tanew 1988), involving 106 patients, two doses of 5-MOP (0.6 mg/kg and 1.2 mg/kg: see above) were compared with 8-MOP 0.6 mg/kg. They found no difference in the mean cumulative UVA dose required to achieve clearance between 8-MOP, 0.6 mg/kg (45 ± 32 J/cm^2) and 5-MOP 1.2 mg/kg (53 ± 33 J/cm^2), but the lower dose of 5MOP, 0.6 mg/kg, required a much larger mean dose of UVA (132 ± 87 J/cm^2). Berg and Ros (Berg 1994), on the other hand, in a trial involving 38 patients, observed lower success rates at both six and nine 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 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 was given at 2 hours. Side-effects (severe erythema, pruritus and nausea) were reported in 18 patients receiving 8-MOP but only in 4 patients receiving high dose 5-MOP and in no patients receiving low dose 5-MOP. 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 (Collins 1996) reported no difference in the success rates (RD = 0.03, 95% CI -0.14 - 0.20) in a trial involving 74 patients. 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 (Buckley 1995), in a trial involving 83 patients also found no difference in success rates (RD = 0.03, 95% CI -0.12 - 0.18). They showed that the MPD group took significantly longer to clear (50.0 days, 95% CI 43.0 - 66.0 vs. 41.0 days, 95% CI 36.0 - 50.0; $p<0.05$) and, again, required a higher median cumulative UVA dose (78.5 J/cm^2 95% CI 59.5 - 113.0 vs. 66.5 J/cm^2 95% CI 44.0 - 90.0) although this 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 - 112.5 vs 55.8 J/cm^2 95% CI 36.5 - 71.5; $p< 0.05$).

RCTs involving topical psoralens

Bath PUVA versus oral PUVA

Two trials compared bath PUVA with oral PUVA. Collins and Rogers (Collins 1992), in a trial involving 44 patients, showed no difference in success rates between bath (8-MOP) and oral (8-MOP) PUVA (RD = 0, 95% CI -0.28 - 0.28). A 4-fold difference in cumulative UVA dose (14.5 ± 9.8 J/cm^2 for bath PUVA and 60.1± 25.4 J/cm^2 for oral PUVA) was reported. Similarly, in a trial involving 93 patients, Turjanmaa and colleagues (Turjanmaa 1985) compared trioxsalen bath PUVA with oral 8-MOP and showed no difference in success rates (RD = -0.02, 95%CI -0.17 - 0.13) but a similar reduction in mean cumulative UVA dose required for clearance (23.5 J/cm^2, range 0.7 - 143 vs. 131.1 J/cm^2 range 7.5 - 543).

Bath (5-MOP) PUVA versus bath (8-MOP) PUVA

Calzavara-Pinton and colleagues, in a trial involving 10 patients (Calzavara-Pinton 1997) 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 (56.8 ± 39.2 SD vs. 59.1± 27.9 SD J/cm^2) or number of exposures (20.0 ± 5.7 vs. 21.6 ± 4.7), however, given the numbers involved, it is unlikely that this trial would have had the power to detect the modest difference that might have been expected.

10.3.2 RCTs comparing UVB phototherapy treatment schedules

Table 10.3 shows the results of the five trials that compared UVB treatment schedules. All five trials used a randomised left/right comparison and 107 patients were randomised. Larkö (Larkö 1989), Picot (Picot 1992) and Storbeck (1993) compared NBUVB with conventional broad band (BBUVB) in left/right randomised studies. From the data reported it was not possible to calculate response rates in the two groups (sides). In Larkö's study, both sides improved and no differences were recorded in symptom scores (erythema, infiltration, desquamation and itching). The low power of the lamps used in this trial meant that irradiation times with NBUVB 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 4.8J/cm^2 for BBUVB). Storbeck and colleagues compared NBUVB and BBUVB but also allocated 13 of 23 patients to receive dithranol treatment. Narrow-band UVB was reported to be more effective. The mean cumulative UVB doses were 14.68 ± 9.84 J/cm^2 (NBUVB) and 1.43 ± 1.13 J/cm^2 (BBUVB). Picot and colleagues reported average reductions in PASI score of 78.5% (NBUVB) and 73.9% (BBUVB). These differences were reported to be statistically significant ($p<0.01$), however, results are reported for 15 patients although 21 were originally enrolled. No details are given about the reasons for withdrawal from the study. In the absence of further detail it is difficult to be confident in the authors' conclusion that NBUVB is more effective than BBUVB. 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 was due to the rarity and mildness of episodes of erythema caused by TL-01 lamps (NBUVB), allowing steady increases in UV dose.

The two other studies compared different regimens for NBUVB. Dawe and colleagues (Dawe 1998) compared a fixed number of UVB exposures delivered either as a thrice weekly or 5-times weekly regimen. Psoriasis cleared more quickly with the 5-times weekly regimen but this was achieved at the expense of a higher UVB dose and more treatments. Expressed in multiples of the individuals' MEDs, the 5-times-weekly sides received a median UVB dose of 94 (range 27-164) compared with 64 (range 23-125) for the 3-times-weekly sides. Hofer and colleagues (Hofer 1998) compared NBUVB regimens with initial doses 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 - 0.12). The group that had started with low-intensity irradiation required a median of 16 treatments compared with 12 but received a total cumulative UV dose of 9.1 J/cm^2 (range 6.28 - 24.32) compared with 14.0 J/cm^2 (range 7.29 -21.7) for the group that had the high-intensity starting dose.

10.3.3. RCTs Comparing PUVA with other phototherapy schedules

Five trials compared PUVA with other phototherapy schedules (Table 10.4). Van Weelden (Van Weeldon 1990) compared oral 8-MOP PUVA with NBUVB. In this trial the therapeutic effectiveness of the two treatments was compared by means of "overall impression", in a left/right comparison in 10 patients. Seven patients preferred NBUVB and three preferred PUVA. Neither total UV doses nor the number of exposures were reported. De Berker and colleagues (de Berker 1997) compared oral PUVA with psoralen plus NBUVB (PNBUVB). in 100 patients. There was no difference in success rates (RD = -0.12 95% CI -0.28 - 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 in the UVB group.

Two trials compared PUVA, using topical 8-MOP, with UVA alone. Pai and Srinivas (Pai 1994) reported a success rate difference of 0.67 (95% CI 0.38 - 0.96), using a "bathing suit" delivery system. Mizuno and colleagues (Mizuno 1980) compared PUVA using topical 8-MOP lotion with UVA and a placebo solution but the results were not extractable.

Van Weelden and colleagues (Van Weeldon 1980) compared oral 8-MOP PUVA with combined UVB plus UVA given with placebo capsules (pUVAB). There was no difference in the mean number of exposures required to achieve 80% clearance (25 ± 5 for PUVA and 28 ± 6 for pUVAB). The average final doses of UVA were similar (14.4 ± 1.6 J/cm^2 for the PUVA group vs 13.2 - 13.8 J/cm^2 for the pUVAB group) however the pUVAB group also received an average final dose of 2416 ± 693 mJ/cm^2 of UVB. The authors concluded that UVB + UVA phototherapy was as effective as oral PUVA. It is not possible to determine how either of these schedules compares with BBUVB alone.

10.3.4. RCTs comparing phototherapy and retinoids with phototherapy or retinoids

Trials comparing phototherapy and retinoids with phototherapy or retinoids are summarised in Table 10.5. The results have been described in detail in Chapter 8.

10.3.5 RCTs comparing photochemotherapy using sunlight as the UV source

Three trials used natural sunlight as the UV light source (Table 10.5). Two trials, involving a total of 52 participants compared sunlight plus psoralen with sunlight alone and one trial compared two different psoralens. None of the trials compared the effects of natural sunlight with artificial radiation. Sehgal and Parikh (Sehgal 1981) showed that 8-MOP and trimethyl-psoralen were equally effective, although the response rates in both groups were low (6/17 vs 6/23). Sadananda-Naik (Sadananda-Naik 1981) showed that the combination of natural sunlight and an unspecified psoralen was considerably more efficacious for clearing psoriasis than sunlight alone. (RD 0.6, 95% CI 0.39 – 0.81)

10.3.6 RCTs comparing phototherapy and/or topical treatment schedules

Eighteen trials in which phototherapy was compared with various forms of topical therapy or combined topical and phototherapy were located. They are summarised in Table 10.6

Phototherapy or photochemotherapy vs. dithranol

Larkö (Larkö 1983) compared a special formulation of dithranol (Psoradrate®) with UVB in a trial involving 100 participants. Success rates were unfortunately not reported.

Rogers and colleagues (Rogers 1979) and Vella-Briffa and colleagues (Vella-Briffa 1978) reported different aspects of the same trial comparing PUVA with a standard dithranol regimen. There were 224 participants in the trial. The response rates for both treatments were high (0.91[PUVA] vs 0.82 [dithranol]) but the time required for clearance was significantly greater in the PUVA-treated group (34.4 ± 1.8 (se) days [PUVA] vs 20.4 ± 0.9 (se) days [dithranol]).

Treatment schedules involving phototherapy and dithranol

Five trials compared different combinations of phototherapy with dithranol. Three involved the use of UVB and one the use of PUVA. Brandt (Brandt 1989) 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 sub-erythematous UVB (seUVB) starting before dithranol treatment or minimally erythematous UVB (meUVB) 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 seUVB group (4.9 weeks) than in the meUVB group (6.2 weeks). Christensen and colleagues (Christensen 1989) compared the combination of UVB with either micro-encapsulated dithranol 1% or extemporaneously prepared 1% dithranol in a left/right, within-patient trial. There was no difference between the treatments,

both clearing psoriasis in 21 of 37 patients in a period of 2-6 weeks. Paramsothy and colleagues (Paramsothy 1988) compared short contact dithranol in combination with tar and UVB with short contact dithranol in combination with an emulsifying ointment bath in a trial involving 53 participants. There was no difference in success rates (RD 0.12 95% CI –0.13-0.37) but the UVB treatment regimen appeared to postpone relapse (10.6 weeks versus 18.9 weeks, $p<0.05$). Morison and colleagues (Morison 1978) compared concurrent PUVA and dithranol with PUVA preceded by 6 weeks of dithranol treatment. Although there was no difference in success rates, (RD –0.11, 95% CI –0.37 – 0.15) the concurrent treatment cleared psoriasis in 60 days compared to 108 days. The corresponding cumulative UVA doses were 12 (range 4-35) J/cm^2 compared to 13 (range 5-27) J/cm^2.

In each of these trials it appears that the addition of phototherapy reduced response time or, in the case of Morison, prolonged remission..

Treatment schedules involving phototherapy and tar

Three trials compared phototherapy treatment schedules with and without tar. Menkes and colleagues (Menkes1985) compared suberythematous UVB in combination with tar oil with maximally erythematous UVB and emollients. There was no difference in success rates but the cumulative UV dose required for clearance was significantly lower for patients treated with tar oil (2.53 vs 4.57 J/cm^2, $p<0.05$). Morison and colleagues (Morison 1978) compared concurrent PUVA and tar with PUVA preceded by six weeks of tar treatment. As only two patients were entered into the sequential arm of the study it is difficult to draw conclusions from this study. Similarly, a study by Williams (Williams 1985) comparing PUVA with a UVB and tar combination involved only six participants, and so it was not possible to draw any firm conclusions.

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 analogue alone.

Two trials, involving 127 participants, compared the combination of PUVA and calcipotriol (D-PUVA) with PUVA and placebo cream. Aktas and colleagues (Aktas 1995), in the smaller of the two trials (20 participants) reported no difference between the two treatments but Frappaz and colleagues (Frappaz 1993) showed a success rate difference of 0.19 (95% CI 0.01 -0.37). In this trial the cumulative UVA dose was significantly lower in the D-PUVA group (30 J/cm^2 vs 57 J/cm^2, $p= 0.021$)

One trial compared the combination of NBUVB phototherapy and calcipotriol with phototherapy alone. (Bourke 1997) Although success rates could not be extracted from their trial, Bourke and colleagues reported a significantly greater fall in PASI in the group receiving combination treatment than in the group receiving UVB alone.

Three trials (Kragballe 1990, Kerscher 1994, Molin 1993) compared combinations of calcipotriol and either BBUVB or NBUVB with calcipotriol alone. In each trial, the combination was reported to be superior to treatment with calcipotriol alone. The trial reported by Kragballe did not demonstrate a success rate difference between the two treatments (RD = 0.2, 95% CI -0.06 - 0.46).

Röcken and colleagues (Röcken 1998) 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 after three weeks.

Treatment schedules involving phototherapy and steroids

Five trials compared combinations of phototherapy and topical steroids with a variety of comparators. Three concerned combinations with UVB phototherapy and two involved PUVA. Larkö and colleagues (Larkö 1984) compared the combination of UVB and clobetasol propionate with each treatment alone. The success rate differences did not differ between the three treatments. Lidbrink and colleagues (Lidbrink 1986) 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 (Horwitz 1985) examined the effects of the addition of steroid (hydrocortisone valerate) to a combination of sub-erythematous 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 versus 17.9 weeks for the control group). Hanke and colleagues (Hanke 1979) 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 26.5 - 171.5] versus 133.71 J/cm^2 [range 44.5 -284]). Morison and colleagues (Morison 1978) 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 (11J/cm^2, range 3-25 compared to 12J/cm^2, range 0-18) although the sequential treatment took longer to clear psoriasis (108 days vs 59 days)

Treatment schedules involving phototherapy and fish oil

Gupta and colleagues (Gupta 1989) examined the effects of the addition of fish oil to low dose UVB phototherapy. Treatment success rates could not be extracted from this trial.

10.4 Withdrawal from treatment due to adverse effects or lack of efficacy

It was not within the scope of this study to extract data on withdrawals from treatment due to adverse effects or lack of efficacy.

10.5 Sources of heterogeneity

It was not possible to pool any of the data from the trials identified because of marked heterogeneity of trial design. The sources of heterogeneity included initial severity of disease, phototherapy doses and regimens, success criteria, duration of treatment, the mix of psoriasis sub-types, the mix of skin types and compliance. Because of these factors and the small size of many of the trials, conclusions can only be tentative.

10.6 Discussion

PUVA

Although PUVA is a well-established treatment for psoriasis only one trial comparing oral PUVA with UVA alone was located (Pai 1994) and one trial comparing topical PUVA with UVA alone. As expected, these trials showed that UVA alone did not clear psoriasis.

Oral PUVA was first used in 1974 (Parrish 1974) when randomised controlled trials were rapidly gaining acceptance as the standard means of assessment for new treatments. The absence of a number of RCTs here probably reflects the fact that different standards have been applied to the adoption of 'instrumental' techniques for treatment. Furthermore, the market for psoralens in small and the products have not been attractive to any major pharmaceutical company. In the UK, psoralens are still unlicensed medicines.

A number of trials were concerned with comparisons of PUVA treatment schedules. Broadly, these were designed to elucidate the optimum dose and mode of delivery of psoralen and the most effective way of dosing UVA. The trials showed that PUVA using 8-MOP or 5-MOP in doses of 0.6 -1.2 mg/kg was effective in clearing psoriasis. There was a dose-response relationship and the dose of psoralen appeared to be inversely related to the dose of UVA required. PUVA using topical

psoralen ("Bath PUVA") was as effective as oral PUVA but required a lower cumulative UVA dose (Collins 1992, Turjanmaa 1985). This is an important observation that could be used to justify greater use of bath-PUVA. Other arguments in favour of bath-PUVA include the fact that patients receiving oral PUVA are obliged to wear sunglasses (to minimise the risk of cataract formation) and avoid sunlight on the day of treatment (to avoid accidental sunburn) and suffer occasional nausea from the oral psoralen.

Two trials (Collins 1996, Buckley 1995) had compared dosing of UVA according to MPD with dosing based on skin type and had produced conflicting results. Both trials showed that the MPD-dosed group required a higher cumulative UVA dose but in the earlier trial (Buckley 1995) more treatments were required and in the later trial (Collins 1996) fewer treatments were required. The explanation for these observations is not clear. Both trials had similar proportions of participants with skin types I and II (approximately 66%) and similar total numbers, however, Buckley used a parallel group design and Collins used a half-body, within-patient comparison. Clearly, Collins and colleagues had the stronger design and so their results should be given greater weight.

UVB

UVB has been used in the treatment of psoriasis for many decades. No trials comparing UVB with placebo were located. This presumably reflects the established position of UVB in the conventional treatment hierarchy for psoriasis.

It has been suggested that "narrow-band" UVB (311nm) offers the possibility of clearance with fewer episodes of erythema and, possibly, a lower cumulative dose of UVB. The five trials that were found concerned comparisons of UVB and narrow-band UVB and comparisons of dosing methods for NBUVB. Comparisons of UVB and NBUVB suggested that NBUVB was at least as effective as BBUVB and was associated with a lower risk of burning, allowing a progressive increase in dose. This might explain why, in two trials, the cumulative dose of UVB was higher using NBUVB.

The two trials that examined dosing methods for NBUVB produced broadly concordant results (Dawe 1998, Hofer 1998). They showed that clearance could be accelerated but only at the expense of a higher UVB dose and more exposures. Given the presumed (but unknown) carcinogenicity of UVB most photobiologists would recommend the lowest dose that produces the desired effect. On the basis of these trials, three-times-weekly dosing could be recommended, starting with doses of less than 70% of the MED.

Other trials

On the basis of the trials located the following tentative conclusions can be drawn:

It is not known how narrow-band or broad-band UVB compares with PUVA. UVB plus UVA may have similar efficacy to PUVA.

PUVA or UVB in combination with retinoids appears to be more effective than either treatment alone (discussed in detail in Chapter 8). Furthermore, the combination of systemic retinoids, i.e. acitretin or etretinate, with PUVA reduces the cumulative dose of PUVA required for clearance and it has been suggested that this may slow the development of skin cancers.

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

One trial shows 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 vitamin D_3 analogues suggest that the combinations are superior to each agent alone.

Combinations of phototherapy or photochemotherapy with topical steroids suggest that the combinations are superior to each agent alone.

10.7 Conclusions

Although it is not possible to derive effect sizes for PUVA, BBUVB or NBUVB from placebo-controlled trials, the response rates in the arms of trials that have used these treatment modalities suggest that all three are able to clear psoriasis in 80-90% of patients treated. The major concern with the use PUVA, particularly in the long-term, is the increased incidence of non-melanoma skin cancer. For this reason guidelines recommend that the maximum cumulative UVA dosage should not exceed 1000 J/cm^2. NBUVB holds the promise of effective treatment without the risk of burning associated with BBUVB. It is also attractive to patients because treatment does not involve tablets or baths. However, the risks of skin cancer with BBUVB and NBUVB are as yet unknown. Although UVB does not penetrate the skin to the same depth as UVA, it is much more energetic and capable of altering DNA directly (Ortel 1998)). Long-term surveillance will be needed to determine the level of risk associated with its use. In the meantime long-term and short-term randomised, controlled trials are required to compare PUVA and NBUVB.

Table 10.2: Psoralen photochemotherapy: Trials comparing treatment schedules

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	Secondary outcome
UVA + oral psoralen							
Andrew 81	PUVA 3/wk 40 mg 8-MOP	PUVA 3/wk 10 mg 8-MOP	26:30	major improvement or full remission after 12 treatments *(see notes)*	24/26 :6/30	0.72 (0.54 - 0.90)	**Cumulative UVA dose** 54.0 J/cm^2; range 14.5 – 115 vs. 77.0 J/cm^2; range 46-113
Berg 94	PUVA 2/wk 5-MOP 1.2 mg/kg	PUVA 2/wk 8-MOP 0.6 mg/kg	19:19	modified PASI (0 -108) "healed or nearly healed"	6/19:12/19 6 weeks 10/19:14/19 9 weeks (extracted results)	-0.31 (-0.58 - -0.04) -0.21 (-0.48 - 0.06)	**Cumulative UVA dose** 187 vs 155 J/cm^2, p<0.05 **Time to clearance** 68 vs 61 days, p<0.05
Buckley 95	PUVA 2/wk using MPD	PUVA 3 /wk dose based on skin type	42:41	Clearance (complete resolution or <1% BSA affected)	37/38:35/37	0.03 (-0.12 – 0.18)	**Time to clearance** 50.0 days, 95% CI 43.0 - 66.0 vs. 41.0 days, 95% CI 36.0 - 50.0; p<0.05 **Cumulative UVA dose (median)** 78.5 J/cm^2 95% CI 59.5 - 113.0 vs. 66.5 J/cm^2 95% CI 44.0 - 90. NS
Collins 96	PUVA minimal phototoxic dose 2/wk; 8-MOP	PUVA skin type based dose 2/wk; 8-MOP	37:37	clearance ± minimal residual activity	31/37:30/37	0.03 (-0.14 - 0.20)	**Number of exposures** (11 vs. 14) **Cumulative UVA dose** 62.9 J/cm^2 vs. 39.5 J/cm^2
Lowe 87	PUVA 3/wk liquid 8-MOP	PUVA 3/wk crystalline 8-MOP	25:22	marked improvement or complete clearing with 20 treatments or fewer	20/25:12/22	0.25 (-0.01 - 0.51)	**Cumulative UVA dose** 68.7 J/cm^2 (liquid) vs 80.8 J/cm^2 (crystalline)

Table 10.2 continued

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	Secondary outcome
Tanew 88	PUVA 4/wk 5-MOP caps 0.6 mg/kg	PUVA 4/wk 8-MOP caps	58:48	complete clearing	55/58:48/48	0.05 (-0.11 - 0.01)	**Cumulative UVA dose ± SD** 45 ± 32 J/cm^2 (8-MOP, 0.6 mg/kg) vs. 53 ± 33 J/cm^2 (5-MOP, 1.2 mg/kg)
Tanew 88	PUVA 4/wk 5-MOP caps 0.6 mg/kg	PUVA 4/wk 5-MOP caps 1.2 mg/kg	58:63	complete clearing	55/58:63/63	0.05 (-0.11 - 0.01)	**Cumulative UVA dose ± SD** 132 ± 87 J/cm^2 (0.6 mg/kg) vs. 53 ± 33 J/cm^2 (1.2 mg/kg)

Table 10.2 continued

UVA + topical psoralen							
Calzavara-Pinton 97	PUVA 4/wk 8-MOP, bath	PUVA 4/wk 5-MOP, bath	5:5	PASI - no threshold reported	not extractable – all patients treated until cleared		**Cumulative UVA dose ± SD** 56.8 ± 39.2 vs. 59.1± 27.9 J/cm^2 **Time to clearance** 20.0 ± 5.7 vs. 21.6 ± 4.7 days
Collins 92	PUVA 3/wk 8-MOP, bath	PUVA 3/wk 8-MOP, oral	22:22	clearance	14/22:14/22	0 (-0.28 - 0.28)	**Cumulative UVA dose** 14.5 ± 9.8 J/cm^2 (bath PUVA) vs. 60.1± 25.4 J/cm^2 (oral PUVA)
Turjanmaa 85	PUVA 3/wk bath	PUVA 3/wk oral	50:43	excellent or good	42/50:37/43	-0.02 (-0.17 - 0.13)	**Cumulative UVA dose** 23.5 J/cm^2, range 0.7 - 143 (bath PUVA) vs. 131.1 J/cm^2 range 7.5 – 543 (oral PUVA)

Notes:

Andrew 81 Patients were initially randomised to 10mg or 40 mg dose of 8-MOP; those on 10mg who did not respond after 12 treatments were then given larger doses (up to 40 mg).

Table 10.3: Trials comparing UVB phototherapy treatment schedules

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	Secondary outcome
Dawe 98	NBUVB 3/wk	NBUVB 5/wk	21:21	clearance or minimal residual activity	not extractable - all patients treated until cleared		**Cumulative UVB dose MED multiples** 64 (range 23-125) vs 94 (range 27-164) **Time to clearance median** 40 vs 35 days, p=0.007 **Number of exposures median** 17 vs 23.5, p=0.01
Hofer 98	NBUVB "far" (low intensity) 3-5/wk	NBUVB "near" (high intensity) 3-5/wk	13:13	≥ 75% decease in PASI	3/13:6/13	-0.23 (-0.58 - 0.12)	**Cumulative UVB dose** 9.1 J/cm^2 (range 6.28 - 24.32) vs. 14.0 J/cm^2 (range 7.29 -21.7), p=0.088 **Number of exposures median** 16 vs 12, p=0.22
Larkö 89	NBUVB 3-5/wk	UVB 3-5/ wk	29:29	not explicitly reported group results reported	not extractable		**Cumulative UVB dose** 0.83 J/cm^2 (NBUVB) vs. 4.8J/cm^2 (BBUVB)
Storbeck 93	NBUVB 3-5/wk	UVB 3-5/wk	23:23	NR	not extractable		**Cumulative UVB dose** 14.68 ± 9.84 J/cm^2 (NBUVB) vs. 1.43 ± 1.13 J/cm^2 (BBUVB)
Picot 92	NBUVB 3/wk	UVB 3/wk	21:21	not explicitly reported group results reported	not extractable		**Cumulative UVB dose** 15.1 ± 3.8 J/cm^2 (NBUVB) vs. 7.6 ± 4.2 J/cm^2 (BBUVB)

Table 10.4: Trials comparing PUVA with other phototherapy schedules

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	Secondary outcome
Mizuno 80	PUVA, 8-MOP topical	UVA + placebo solution	not extractable (111 patients in total)				
Pai 94	PUVA 3/wk	UVA 3/wk	12:12	NR	9/12:1/12	0.67 (0.38 - 0.96)	
Van Weeldon 90	PUVA 2/wk	NBUVB 2/wk	10:10	overall impression	not extractable		
Van Weeldon 80	PUVA 2/wk	PLO caps + UVA +UVB	15:15	NR	not extractable- all patients treated until cleared		**Number of exposures** *25 ± 5 (PUVA) vs. 28 ± 6 (pUVAB)* **Cumulative UVA dose** 14.4 ± 1.6 J/cm^2 (PUVA) vs. 13.2 - 13.8 J/cm^2 (pUVAB) **Cumulative UVB dose** 2416 ± 693 mJ/cm^2(pUVAB) **Time to clearance** 5.2 ± 2.8 (PUVA) vs.5.4 ± 4.3 (pUVAB) months
de Berker 97	PUVA 2/wk	PNBUVB 2/wk	50:50	All exposed lesions above knees cleared	37/50:43/50	-0.12 (-0.28 - 0.04)	

Table 10.5: Trials comparing phototherapy with retinoids (includes UV vs retinoids and UV + retinoids vs other treatments)

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)
Lauharanta 89	bath PUVA 3/wk + Aci	bath PUVA 3/wk + Etr	17:17	≥ 90% decrease in PASI	17/17:17/17	
Lauharanta 81a	PUVA up to 3/wk	Etr alone then Etr+PUVA	20:20	≥ 75% decrease in PASI	19/20:18/20	0.05 (-0.11 - 0.21)
Lauharanta 81b	PUVA up to 3/wk	Etr alone then PUVA	20:20	≥ 75% decrease in PASI	19/20:17/20	0.1 (-0.08 – 0.28)
Lauharanta 81c	PUVA up to 3/wk	Etr	20:20	≥ 75% decrease in PASI	19/20:13/20	0.30 (0.07 –0.53)
Parker 84	PUVA + Etr	PUVA + PLO	15:15	clearance (≡ less than 2% BSA affected)	14/15:9/15	0.33 (0.05 -0.61)
Saurat 88a	PUVA 3/wk + Etr	PUVA 3/wk + PLO	23:22	≥ 75% decrease in PASI	17/20: 16/22	0.12(-0.12 - 0.36)
Saurat 88b	PUVA 3/wk + Etr	PUVA 3/wk + Aci	23:20	≥ 75% decrease in PASI	16/23: 16/22	-0.03(-0.30 - 0.24)
Sommerburg 93	PUVA 3-5/wk + Aci	PUVA 3-5/wk + PLO	44:44	≥ 75% decrease in PSI	28/44:19/44	0.2 (-0.01 - 0.41)
Tanew 91	PUVA 2/wk + Aci	PUVA 2/wk + PLO	30:30	≥ 90% clearance of psoriasis	22/30:20/30	0.06 (-0.17 - 0.29)

Table 10.5 continued

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)
Green 92a	PUVA 2/wk + Etr	NBUVB 3/wk + Etr	15:15	"satisfactory response"	14/15:12/15	0.13 (-0.11 - 0.37)
Green 92b	PUVA 2/wk + Etr	NBUVB 3/wk	15:15	"satisfactory response"	14/15:15/15	-0.07 (-0.20 - 0.06)
Lowe 91	ACI + UVB	PLO + UVB	16:18	not reported	not extractable	
Ruzicka 90	ACI + UVB	PLO + UVB	42:40	≥ 75% decrease in PASI	24/42:9/40	0.34 (0.14 - 0.54)
Iest 89a	ACI + UVB	ACI	9:9	clearance ≥ 80% clearance of lesions	8/9:2/9	0.67 (0.33 - 1.01)
Iest 89b	ACI + UVB	UVB	9:32	clearance ≥ 80% clearance of lesions	8/9:20/32	0.26 (0.00 - 0.52)

Table 10.6: Trials of psoralens using natural sunlight as the UV source

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)
Parrish 77	Sun + 8-MOP	Sun + PLO	6:6?			
Seghal 81	Sun + 8-MOP	Sun + TMP	17:23	≥ 75% improvement	6/17:6/23	0.09 (-0.02 -0.38)
Sadananda-Naik 81	Sun + psoralen	Sun +PLO	20:20	≥ 95% improvement	12/20:0/20	0.6 (0.39 - 0.81)

Table 10.7: Trials of combined phototherapy and topical treatment schedules

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	
Phototherapy vs dithranol							
Larkö 83a	UVB 3/wk	dithranol 0.2% (Psoradrate 0.2%®)	50:50	chronic, symmetrical psoriasis	not extractable		
Larkö 83b	UVB 3/wk	placebo cream	50:50	chronic, symmetrical psoriasis	not extractable		
Rogers 79 + Vella-Briffa 78	PUVA 3/wk	dithranol daily	113:111	clearance = plaques flat, and not scaly or erythematous	103/113:91/111	0.09 (0.00 - 0.18)	**Time to clearance** 34.4 ± 1.8 (se) days (PUVA) vs 20.4 ± 0.9 (se) days (dithranol)
Treatment schedules involving phototherapy and dithranol							
Brandt 89	UVB pre-treatment + dithranol	Dithranol + UVB post-treatment	15:15	NR	not extractable		**Time to clearance** 4.9 weeks (seUVB) vs. 6.2 weeks (meUVB)
Christensen 89	UVB + micro-encapsulated dithranol 1% (see notes)	UVB + extemporaneously prepared dithranol 1% (see notes)	37:37	Severity score <1 (scale 0-4)	21/37:21/37	0 (-0.23 –0.23)	

Table 10.7 continued

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	
Morison 78a	daily dithranol for 6 wks then PUVA 2/wk (see notes)	daily dithranol and PUVA 2/wk (see notes)	19:20	clearance - ≤ 1% BSA involved	16/19:19/20	-0.11 (-0.30 - 0.08)	**Time to clearance** 108 days vs. 60 days **Cumulative UVA dose** 12 (range 4-35) J/cm^2 vs. 13 (range 5-27) J/cm^2.
Paramsothy 88	dithranol + tar +UVB	dithranol + emusifying ointment bath	27:26	clearance - ≤ 3% BSA involved	20/27:16/21	0.12 (-0.13 - 0.37)	**Time to relapse** 10.6 weeks vs. 18.9 weeks, p<0.05
Storbeck 93	NBUVB or BBUVB	NBUVB or BBUVB with dithranol	10:13	NR	not extractable		
Treatment schedules involving phototherapy and tar							
Menkes 85	Sub-erythematous 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 – 0.15)	**Cumulative UVB dose** 2.53 vs 4.57 J/cm^2, p<0.05
Morison 78b	daily tar for 6 wks then PUVA 2/wk	PUVA 2/wk + daily tar	2:19	clearance - ≤ 1% BSA involved	2/2:16/19	0.16 (0.00 – 0.32)	
Williams 85	PUVA 2/wk	UVB + tar 5/wk	4:2	6pt scale: considerable improvement/clear	2/4:0/2	0.5 (0.01 – 0.99)	

Table 10.7 continued

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	
Treatment schedules involving phototherapy and vitamin D analogues							
Aktas 95	PUVA + calcipotriol	PUVA + PLO	10:10	NR	not extractable		
Bourke 97	calcipotriol 100g/wk + NBUVB 3/wk	calcipotriol 100g/wk	10:10	NR	not extractable		
Bourke 97	calcipotriol 100g/wk + NBUVB 3/wk	NBUVB 3/wk	10:10	NR	not extractable		
Frappaz 93	PUVA + calcipotriol	PUVA + placebo ointment	54:53	≥ 75 decrease in PASI	40/54:29/53	0.19 (0.01 -0.37)	**Cumulative UVA dose 30 J/cm^2 vs 57 J/cm^2, p= 0.021**
Kragballe 90	UVB + calcipotriol	calcipotriol	20:20	clear - global assessment	7/20:3/20	0.2 (-0.06 -0.46)	
Röcken 98	Tacalcitol +NBUVB 3-5/wk	Tacalcitol	24:24	NR	not extractable		

Table 10.7 continued

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	
Treatment schedules involving phototherapy and steroids							
Hanke 79	PUVA + betamethasone valerate 0.1%	PUVA + Eucerin oint.	12:12	clearance - 6 point scale	12/12:12/12 *see notes*		**Cumulative UVA dose** 69.96 J/cm^2 (range 26.5-171.5) vs. 133.71 J/cm^2 (range 44.5-2840
Horwitz 85	Sub-erythematous UVB +tar + hydrocortisone valerate cream	Sub-erythematous UVB +tar + cream vehicle	10:9	clearance = reduction in global severity score to less than 10% of VAS	3/10:1/9	0.19 (-0.16 - 0.54)	**Duration of remission** 5.9 vs. 17.9 weeks
Lärko 84	clobetasol propionate +UVB 3/wk	vehicle + UVB 3/wk	30:30	healed = disappearance of scaling, infiltration and erythema	18/30:20/30	-0.07 (-0.31- 0.17)	
Lärko 84	clobetasol propionate +UVB 3/wk	clobetasol propionate	30:30	healed = disappearance of scaling, infiltration and erythema	18/30:13/30	0.17 (-0.08 - 0.42)	
Lidbrink 86	UVB + dithranol 5/wk clobetasol propionate	UVB + dithranol 5/wk	26:24	complete clearance = only slight erythema remaining ≤ 5pts (scale 0-30)	18/26:15/24	0.06 (-0.20 – 0.32)	**Time to heal** 2.5 vs 4.0 weeks

Table 10.7 continued

Reference	Intervention	Comparator	Numbers (intervention: comparator)	Success criterion	Response rates	Rate difference (95%CI)	
Morison 78c	daily fluocinolone acetonide for 6 wks then PUVA 2/wk	PUVA 2/wk + daily fluocinolone acetonide	19:19	clearance - ≤ 1% BSA involved	17/19:19/19	-0.11 (-0.25 - 0.03)	**Cumulative UVA dose** 11 J/cm^2 (range 3-25) vs. 12 J/cm^2 (range 0-18) **Time to clearance** 108 vs. 59 days
Treatment schedule involving phototherapy and fish oil							
Gupta 89	UVB 2/wk + fish oil caps bd	UVB 2/wk + PLO caps bd	10:10	6 point scale	not extractable		

Chapter 11

Therapeutic Gain and NNTs

Summary

Therapeutic gain' is a term that can be used to describe the difference between experimental and control treatments. It is also known as the absolute benefit increase (ABI). The reciprocal of the ABI gives the number needed to treat (NNT). ABIs and NNTs have been calculated for treatments for severe psoriasis involving cyclosporin, retinoids, phototherapy and photochemotherapy. The results show that the calculated NNTs mainly fall into the accepted range for effective treatments.

11.1 Description of effect size as therapeutic gain or absolute benefit increase

'Therapeutic gain' is a concept that is particularly relevant to treatments that deliver beneficial effects, such as cure or clearance of disease, rather than those that prevent or delay the occurrence of undesirable effects. It may be defined as the difference between the proportions of patients achieving the effect with the experimental and control treatments. In numerical terms it is the same as the absolute risk difference (or rate difference). Confusion arises because many early studies in the EBM arena were concerned with the effects of treatment on the reduction of risks, for example, the reduced risk of cardiac death following the use of thrombolytic agents. As a result, the absolute risk reduction (ARR) is commonly cited in textbooks. However, when a treatment causes a positive beneficial effect the 'risk' of improvement increases. This could be described as an absolute risk increase, but the terminology is uncomfortable for non-statisticians, and so the term 'absolute benefit increase (ABI)' has been adopted (Sackett 2000). An alternative expression for 'absolute benefit increase' is 'therapeutic gain'. This has the merit that it is immediately understandable for clinicians as it answers the question, 'How many more patients improve on this treatment relative to the control treatment?'

One of the reasons why the ABI is understandable for clinicians is that it distinguishes and preserves the baseline risk, whereas relative descriptions of effect size do not reflect risk of event without therapy and therefore cannot distinguish between large and small treatment effects. For example, a treatment that cures 60% of patients compared with a placebo response rate of 30%, has a relative benefit increase (RBI) of 100%, however, a treatment that cures 1% of patients compared with a placebo response rate of 0.5%, will also have a RBI of 100%. The corresponding ABIs would be 0.3 and 0.005.

The other advantage of the ABI is that it can readily be converted into the 'number needed to treat (NNT)', that is the number of patients that need to be treated in order to achieve one additional beneficial outcome. This is numerically equivalent to the reciprocal of the ABI. Using the figures from the example above, the first case has an ABI of 30% (0.3) which is equivalent to a NNT of four (calculated value = 3.3). By convention, NNTs are always rounded up to the nearest whole number, as it is not possible to treat a fraction of a patient. The second case has an ABI of 0.5% (0.005), which is equivalent to a NNT of 200. These numbers fit comfortably with the intuitive clinical view that a treatment that benefits an extra 30% of patients will bring more clinical 'successes' than one which benefits an extra 0.5% of patients.

The NNT is a derived quantity that relates to the conditions under which the trial was carried out and it has an associated confidence interval that is related to the precision of the original ABI estimate. The confidence interval for the NNT is the reciprocal of the confidence interval for the ABI. (CI: 1/CI ABI_{upper} to 1/CI ABI_{lower}).

The NNT is usually expressed in the form, 'in order to avoid one additional adverse outcome/ achieve one more beneficial outcome, X patients need to be treated with the intervention in question for a period of Y time'. It follows that if a pooled value for the ABI is used then it must be based on reasonably similar trials, otherwise a nonsensical answer will be derived. Once again the issues of heterogeneity, or intrinsic differences in the ways in the trials were designed and carried out, are important. In particular, the periods of treatment need to be similar. (Sackett 2000) describes a method for adjusting NNTs for different follow-up times based on the assumption that the relative risk reduction (RRR) from treatment is constant over time, that is to say, a treatment is assumed to exert the same relative benefit in year one as it does over each of the next few years. Sackett cites the example of treatments for hypertension: treatment of severe hypertension for 1.5 years has a NNT of 3, whereas treatment of mild hypertension for 5.5 years has a NNT of 128. In order to compare these, the results need to be adjusted so that they relate to the same time period, resulting in a hypothetical NNT. In this example, the NNT for treatment of mild hypertension can be adjusted to the hypothetical value for 1.5 years using the formula:

$NNT_{hypothetical} = NNT_{observed} \times$ (observed time/hypothetical time)

Which gives: $NNT_{1.5} = 128 \times (5.5/1.5) = 470$

This means that 470 patients with mild hypertension would need to be treated for 1.5 years to prevent one additional adverse outcome compared with three patients with severe hypertension.

Where positive differences are sought this would equate to an assumption that the RBI is constant over time. Whereas it is reasonable to assume that RRRs may be constant when a preventive treatment is given, it is not reasonable to assume that RBIs are constant when a curative or 'clearing' treatment is given, because these processes have ceilings. It is therefore inappropriate to adjust NNTs for these types of trials in this way.

11.2 Therapeutic gain in severe psoriasis treatment

In chapters 7-10 effect sizes for trials were reported as odds ratios. In this chapter the data will be re-examined to provide ABIs and NNTs. Where possible, summary ABIs have been calculated using data from trials of comparable durations.

11.2.1 Cyclosporin

The ABIs and NNTs for trials using cyclosporin are shown in Table 11.1. The most striking feature of the latter is their small values, which show that only modest numbers of patients need to be treated in order for many patients to experience benefits. For example, the NNT with cyclosporin, in the dose range 2.5 – 7.5 mg/kg/day, for 8-10 weeks, compared with placebo, is two (95% CI 2-4). This means that two patients would need to receive this treatment in order for one to have a successful outcome. NNTs of this order are commonly seen with antibiotic treatments and they contrast markedly with the NNTs seen with preventative treatments (EBM website).

11.2.2 Retinoids

The ABIs and NNTs for trials using retinoids are shown in Table 11.2. Once again, all the NNT values are relatively low, except for the NNT for acitretin compared to etretinate. In this case the value is infinity, indicating that an infinite number of patients would need to be treated with acitretin compared to etretinate in order to achieve one more beneficial outcome. The combination of a retinoid with PUVA (RePUVA), compared with PUVA alone, has an NNT of 9, with a wide confidence interval (5-50). This shows that the additional benefit conferred by the retinoid is relatively small. In practice this would have to be weighed against the risk of additional side effects arising from the retinoid treatment and the further benefit of the reduced UVA dose required by

patients receiving RePUVA (see table 8.13). The effect of adding a retinoid to UVB treatment was larger, giving an ABI of 0.28 and a NNT of 4 (95% CI 3-7).

11.2.3 Phototherapy and photochemotherapy

The ABIs and NNTs for trials using phototherapy or photochemotherapy are shown in Table 11.3. (ABIs and NNTs have been derived only for comparisons in which a difference was shown.) In this series several of the NNTs are derived from single trials and therefore need to be interpreted with caution. The effectiveness of PUVA using 40 mg 8MOP compared to 10mg 8MOP over a four-week period is clearly shown by the NNT of 2 (2-2). Similarly the superiority of PUVA over UVA is shown by the NNT of 2 (1-3). In this latter study the time period for treatment was not reported. Sadananda-Naik (Sadananda-Naik 1981) reported the same phenomenon in a study that compared the effects of sunlight plus psoralen with sunlight alone. Once again, this produced a large ABI (0.60, 95% CI 0.39 – 0.81) and a NNT of 2 (95% CI 2-3).

The effects of adding retinoids to either PUVA or UVB have been discussed above. One series also compared the combination of UVB and acitretin with acitretin alone. As might be expected, the combination was superior, giving an ABI of 0.67 (95% CI 0.33 – 1.01) and a NNT of 2 (95% CI 1-3).

A pilot study comparing PUVA with the Goeckerman regimen recruited only six patients and showed a difference in favour of PUVA. Although the ABI was 0.50, the associated 95% confidence interval was 0.01 - 0.99, suggesting that the size of the true difference is likely to lie anywhere between one and 99 percent. In this case, although the NNT is only 2, the 95% confidence interval is (1-100), showing that it may be necessary to treat 100 patients with PUVA instead of Goeckerman therapy in order to achieve one more beneficial outcome. Both figures clearly illustrate the well-known phenomenon of imprecise estimates arising from small samples.

Frappaz and colleagues (Frappaz 1993) examined the effects of adding calcipotriol ointment to UVA treatment. Over a ten-week treatment period, the ABI was 0.19 (95% CI 0.01 – 0.37) and the NNT was 6 (95% CI 3-100).

11.3 Discussion

The ABI or therapeutic gain is a helpful way of describing the response to treatment in therapeutic trials, because it indicates the additional proportion of patients that is likely to have a beneficial outcome from the active treatment compared with the control treatment.

The NNT provides an intuitively understandable way of describing the impact of treatment. Although it is fundamentally the same information as that provided by the ABI (as it is the reciprocal of the ABI) the fact that it is always expressed as a whole number of patients, makes it easier to relate to the clinical situation. An additional benefit of the NNT is that, in indicating the number of patients that will need to be treated in order for one to benefit, it also shows how many will be exposed to the risks of treatment (without necessarily benefiting) and how many will consume resources in the process of achieving one beneficial outcome. Both of these attributes are useful in clinical decision-making.

Neither the ABI nor the NNT is an answer in itself. In addition to the considerations outlined above they need to be interpreted in the light of the likelihood of harmful effects from a given treatment.

The ideal NNT is 1, that is to say that every patient treated will achieve a beneficial outcome. In practice this is unlikely to occur for a number of reasons. The main reasons are that few treatments are 100% effective and many control groups exhibit some response. The convention of rounding the NNT value up to a whole number of patients means that calculated NNTs of 1.1 and 1.9 will both be rounded up to 2. A more subtle influence is that of intention to treat analysis. The inclusion in the analysis of all the subjects that were originally randomised will almost invariably result in a response rate to active treatment that is less than 100%, and therefore, even in the presence of completely inactive control, it would be impossible to achieve an ABI of 1.

The NNTs calculated for treatments for severe psoriasis were all in the range 2-9. It is recognised that the NNTs for effective treatments are generally in the range 2-4 (Wiffen 2001). It could therefore be expected that the treatments that have been shown to be effective in the treatment of psoriasis in earlier chapters would have NNTs in or near to this range, and it is satisfying to see that this is the case.

11.4 Conclusions

The ABI and NNT provide a useful way if looking at the individual and pooled results of clinical trials. In order to use these indices in clinical practice it is necessary to take into account the factors that influence the ABI and NNT and other aspects of treatment, such as the likelihood of harm and the costs of treatment.

Table 11.1 Numbers needed to treat: Cyclosporin interventions

Interventions compared	Number of series (number of patients)	Doses (mg/kg/day)	Time period (weeks)	ABI Absolute benefit increase (95% CI)	NNT Number needed to treat (95% CI)
Cyclosporin vs placebo or other treatments					
Cyclosporin vs placebo*	6 (236)	1.25 – 7.5	8-10	0.51 (0.28 – 0.74)	2 (2-4)
Cyclosporin vs etretinate	2 (286)	CSA 2.5 –5.0 ETR 0.5 – 0.75	10-12	0.36 (0.14 – 0.58)	3 (2-8)
Cyclosporin vs betamethasone valerate	1 (168)	CSA 5	4	0.41 (0.28 – 0.54)	3(2-4)
Cyclosporin dose comparisons					
Cyclosporin 2.5 mg vs cyclosporin 1.25mg	2 (242)		10-12	0.24 (0.13 – 0.35)	5 (3-8)
Cyclosporin 5.0 mg vs cyclosporin 2.5mg	2 (432)		12	0.28 (0.20 – 0.37)	4 (3-5)
Cyclosporin + calcipotriol combination					
Cyclosporin + calcipotriol vs cyclosporin	1 (69)	CSA 2	6	0.37 (0.17 – 0.57)	3 (2-6)

* Recalculation of the ABI for CSA vs PLO omitting the very low dose (1.25 mg/kg) gives an ABI of 0.56 (0.30 – 0.82) and a NNT of 2 (2-4), and therefore makes no difference.

Table 11.2 Numbers needed to treat: Retinoid interventions

Interventions compared	Number of series (number of patients)	Doses (mg/day)	Time period (weeks)	ABI Absolute benefit increase (95% CI)	NNT Number needed to treat (95% CI)
Retinoid comparisons with other treatments					
Retinoids vs placebo	4 (98)	>50	8-10	0.47 (0.33 – 0.67)	3 (2-3)
Retinoid +PUVA vs PUVA	6 (276)	50 - 60 or 0.75 - 1.0mg/kg	10-12	0.12 (0.02 – 0.22)	9 (5-50)
Retinoid + UVB vs UVB	3 (142)	35 - 50 or 1mg/kg	8-12	0.28 (0.15 – 0.42)	4 (3-7)
Retinoids + topical steroids vs topical steroids	3 (216)	0.66 - 1.0 mg/kg	6-8	0.21 (0.08 – 0.33)	5 (3-13)
Retinoid (ACI) + calcipotriol vs acitretin	1 (135)	20	12	0.26 (0.10 – 0.42)	4 (3-10)
Comparisons of retinoids					
Acitretin vs etretinate	4 (505)	30-50	8-12	0	∞

Table 11.3 Numbers needed to treat: Phototherapy and photochemotherapy interventions

Interventions compared	Number of series (number of patients)	Doses (mg/day)	Time period	ABI Absolute benefit increase (95% CI)	NNT Number needed to treat (95% CI)
PUVA, 40mg 8MOP vs, PUVA 10mg 8MOP (Andrews 81)	1(56)	PUVA 3/wk	4 weeks (12 treatments)	0.72 (0.54 – 0.90)	2 (2-2)
PUVA vs UVA (Pai 84)	1 (24)	UVA 3/wk	NR	0.67 (0.38 – 0.96)	2 (1-3)
Sun + psoralen vs sun + PLO (Sadananda-Naik 81)	1(40)	-	4 weeks	0.60 (0.39 –0.81)	2 (2-3)
PUVA + Retinoid vs PUVA + PLO	6(276)	PUVA 3/wk ETR 0.75 mg/kg	10-12 weeks	0.12 (0.02 – 0.22)	9 (5-50)
UVB + Retinoid vs UVB	3(142)	35 - 50 or 1mg/kg	8-12 weeks	0.28 (0.15 – 0.42)	4 (3-7)
ACI + UVB vs ACI	1(28)	ACI 30 mg/d	Max 30 treatments	0.67(0.33 – 1.01)	2(1-3)
PUVA vs UVB + tar (Williams 85)	1(6)	PUVA 2/wk UVB daily, except weekends	NR	0.50 (0.01 –0.99)	2 (1-100)
PUVA + CPT vs PUVA + PLO (Frappaz 93)	1(107)	PUVA 3/wk	10 weeks	0.19 (0.01 – 0.37)	6 (3-100)

Chapter 12

Observational studies

Summary

This chapter contains reports of two linked observational studies. The first concerned a series of 256 patients for whom standardised psoriasis assessment forms had been completed. The form covered several aspects of disease severity along with details of related factors such as alcohol and tobacco use. Analysis of the data in the forms provided a profile of the types of patient routinely seen in the psoriasis specialist clinic. The second project examined treatment pathways for patients in the first project. Those who were found to have received treatment with cyclosporin, methotrexate, acitretin, PUVA or UVB were selected to determine how for the actual treatment pathways matched those which were assumed in the decision-analytic model proposed by Einarson and colleagues (Einarson 1994).

12.1 Introduction and background

Einarson and colleagues (Einarson 1994) reported an economic analysis that compared four oral treatment regimens (cyclosporin, methotrexate, etretinate and PUVA) for psoriasis. (See Chapter 5) This analysis was based on a decision-analytic model. The treatment pathways were based on published therapeutic guidelines, validated by an expert panel and success rates for treatments were derived from meta-analyses. In the present study, success rates have been derived through a systematic review and, where appropriate, meta-analyses. These have been described in the preceding chapters. This chapter describes two, linked observational studies that were undertaken to test the validity of the assumptions about treatment pathways in the real-life, UK situation.

The setting for these studies was the psoriasis specialty clinic at Hope Hospital in Salford. This weekly clinic is operated by two senior consultant dermatologists, together with Special Practice Registrars and specialist dermatology nurses. The clinic handled exclusively patients with confirmed or presumed psoriasis. Patients were referred by GPs and dermatologists throughout the (former) North West NHS Region. During 1995 a psoriasis assessment form had been developed for routine use for new patients attending the clinic. The form provided a systematic means of gathering large amounts of information about the patients who attended the speciality clinic, at one point in time. It therefore appeared that the psoriasis specialty clinic, with its detailed records, would provide an excellent testing ground to check some of the assumptions made in the published

decision-analytic model. Two studies were undertaken; the first utilised data from the assessment forms to characterise the patient population at one point in time and the second was a longitudinal study in which the progress of patients receiving oral treatments or phototherapy was followed and the outcomes recorded.

A third aspect of the observational studies was concerned with observation and timing of clinic procedures in order to determine resource inputs (staff time and procedures) to patients attending the psoriasis speciality clinic. These will be reported in Chapter 13.

12.2 Psoriasis assessment forms study

12.2.1 Method

Psoriasis assessment forms completed during the two-year period 1st January 1996 to December 31st 1997 were collected. An Access (Microsoft) database was constructed and all the details except for the sketch showing areas of the body affected were entered.

12.2.2 Results

Age and sex distribution

256 assessment forms were completed during the study period. There were 145 male and 111 female patients in this sample and the average age was 40.1 (± 16.5 SD) years.

Types of psoriasis

The most common diagnosis was chronic plaque psoriasis (208 cases) followed by guttate psoriasis (31 cases). Two patients had pustular psoriasis, one was record as flexural psoriasis and no diagnosis was recorded in 14 cases. The age of onset of psoriasis ranged from birth to 76 years with an average of 23.1 years (± 15.4 SD).

Family history of psoriasis

Table 12.1 shows the prevalence of family histories of psoriasis.

Category	Number
First degree relative affected	79
Second degree relative affected	29
First and second degree relatives affected	30
No family history of psoriasis	112
Data missing	6

Approximately 55% of the sample had a relative with psoriasis whilst about 44% reported no family history of the condition.

Arthritis

Sixty-seven patients (26%) were recorded as having arthritis.

Alcohol and tobacco intakes

246 patients provided data on their use of alcohol and tobacco.
Eighty-five patients did not drink alcohol. For those who did, (161 patients) the average number of units of alcohol per week was 19.2 (± 22.2 SD). The distribution of alcohol intake was positively skewed, with a median value of 12.0 and a maximum of 154 units per week.

One hundred and fifty-one patients did not smoke. For the 95 who did, the average number of cigarettes per day was 17.6 (± 9.76 SD). The distribution of cigarette smoking was positively skewed, with a median value of 20.0 and a maximum of 60 cigarettes per day.

PASI scores

PASI scores in the sample ranged from 0 -55 with an average of 8.79 (± 6.65 SD).

12.2.3 Discussion.

Previous studies have shown that psoriasis occurs with the same frequency in men and women (Farber 1974). In this sample, 145 (57%) were male and 111 (43%) were female, which was broadly in line with the expected 50:50 distribution. The mean age of the group was 40.1 years, but the age range was from 16-76 years. This was consistent with the observation that psoriasis can start at any age, although there are two recognised peaks, at 16-22 years of age and at 57-60 years of age, and then follows a relapsing and remitting course (Greaves 1995). It is well known that psoriasis tends to run in families and recent studies have shown associations between psoriasis and human lymphocyte antigen (HLA) markers. (Ortonne 1999). It has been estimated that one third of patients with psoriasis have a positive family history of the condition. (Krueger 1994) In this group, 138 (55%) patients reported having one or more relatives with psoriasis. It is not immediately obvious why this figure should be so high. One explanation could be that the background prevalence of psoriasis is higher in the UK population than in the sample used for the previous estimate. Another possibility is that the specialty clinic was attracting a greater proportion of patients with so-called 'early-onset' psoriasis. Early onset psoriasis starts between the ages of 16 and 22 years, has a strong hereditary association, is frequently associated with the presence of HLA-CW-6 and tends to cause disease of greater severity than the late onset type. (Ortonne 1999) This explanation would also fit with the age profile of the group.

Estimates for the prevalence of arthritis in association with psoriasis vary from 5% (Hunter 1995) to 15% (Stern 1997). In this group, 26% of patients reported having arthritis. It is not clear whether this figure reflects over-reporting or a genuinely high prevalence.
The roles of alcohol and tobacco have been the subjects of much speculation as both are known to be associated with psoriasis. The question of whether there is a causal relationship has not yet been satisfactorily answered, although it has been suggested that smoking might account for as many as a quarter of all cases of psoriasis. (Williams 1994)

The PASI scale runs from 0-72; a value of less than 8 is often used in trials to indicate a minimal level of disease and a value of 20 or more is said to indicate severe disease. The mean PASI score for the group was 8.79, which appears to be low. This may be the result of a number of factors. Given the relapsing and remitting nature of the disease, it may not necessarily have been at its worst when the assessment was made. Alternatively, because the PASI takes no account of the psychological impact of the disease, a low score could, nevertheless, represent disease which is disabling by virtue of being in a visible or distressing place and, finally, it could reflect a good response to treatment prior to the clinic visit. It is of interest that in a systematic study of one GP practice 75 confirmed cases of psoriasis were identified (from a register of 5395) (Nevitt 1996). The distribution of PASI score was positively skewed with a median value of 2.4 and a maximum of 10. Compared with this group, therefore, the present study group had appreciably worse disease.

Overall, the demographic features of the group suggest that the patients attending the psoriasis specialty clinic may be suffering from more severe disease than average. The mean PASI score is not consistent with this assessment but it should be noted that the PASI is useful for monitoring the progress of disease (or response to treatment) rather than for providing an index of the overall severity of the condition.

In summary, the group of patients attending this clinic appeared to be suffering from moderate-severe psoriasis and it was therefore appropriate to use it as the source for information about treatment pathways.

12.3 Treatment pathways study

12.3.1 Method

The medical records for each of the patients in the psoriasis assessment forms study were located and details of the patients' treatment pathways were extracted and recorded on a standard form.

12.3.2 Results

Records were traceable for 166 patients. For the remainder, the records were missing or the patients had been discharge or had died. In addition, a number of records were unavailable because a major project was underway to merge records within the Trust. Part of this involved microfilming the records. Records that had been removed for microfilming were not available for the study.

Forty-eight patients received treatment with oral agents (cyclosporin, methotrexate or etretinate), photochemotherapy (PUVA) or UVB. Several patients received more than one of these treatments.

Methotrexate

Fourteen patients received treatment with methotrexate (7 male, 7 female; average PASI 11.9 ± 1.5 (SEM)). Eight patients were already taking methotrexate at the time of assessment and 6 started treatment after assessment. (See Table 12.2)
On eight occasions methotrexate treatment was discontinued. The reasons for discontinuation were intolerable side effects 4, intercurrent illness 2, restoration of fertility 1, and no reason recorded. Methotrexate was restarted in three patients (those in whom it had been stopped for intercurrent illness or restoration of fertility). In the remaining five cases, one switched to PUVA, three were given topical treatment and one was hospitalised for a severe exacerbation of psoriasis.

The recorded reasons for prescribing methotrexate showed that it was selected for patients with extensive or severe psoriasis when:

- The disease was difficult to treat with topical agents
- There was co-existing arthritis
- Cyclosporin treatment was not appropriate because there was a history of cancer, the patient was too young or did not wish to take cyclosporin
- Other systemic treatments had been ineffective or poorly tolerated

Cyclosporin

Seventeen patients received treatment with cyclosporin (10 male, 7 female; average PASI 21.4 ± 3.3 (SEM)). (See table 12.3) One patient was already taking cyclosporin at the time of assessment and 16 started treatment after assessment. In total there were 25 new courses of cyclosporin.

Fourteen courses were discontinued (9 – clearance of psoriasis, 3 - side effects, 1 – intercurrent illness, 1 - other) and 11 were ongoing. On three occasions cyclosporin was discontinued because of intolerable side effects. In one case methotrexate treatment, which had been successful in the past, was reinstated. In another case, acitretin was prescribed and in the remaining case, although methotrexate was considered, topical treatment was eventually selected in accordance with the patient's preference.

Five patients received more than one course of cyclosporin and each repeat course followed a successful response to cyclosporin.

The recorded reasons for prescribing cyclosporin showed that it was selected for patients with extensive or severe psoriasis when:

- The disease had failed to respond to MTX
- Continued systemic treatment was required and fertility (male) was required.
- MTX was contra-indicated (e.g. because of high alcohol intake)
- The patient was unable to attend for phototherapy
- CSA had been effective in the past
- The patient expressed a marked preference for CSA and was aware of the risks

Acitretin

Six patients received seven course of treatment with acitretin (6 male, 0 female; average PASI 10.0 ± 3.5 (SEM)). Four patients were already taking acitretin at the time of assessment and two started treatment after assessment. (see Table 12.4)
Four courses were discontinued (1- satisfactory response, 1- intercurrent illness (alcohol detoxification), 1- exacerbation of disease, 1- did not attend clinic for assessment and re-supply).
In one case, where there had been a satisfactory response to treatment with acitretin, a further course of the same treatment was recommended in the event of a relapse. In the two other cases, in

which a positive decision to discontinue acitretin was made, alternative treatments were prescribed. In one case this was in-patient treatment using dithranol and UVB and in the other, cyclosporin, which had been effective in the past, was recommenced. In the case where acitretin was discontinued by default, the disease had relapsed and acitretin was reinstated.
In one case where the disease seemed particularly difficult to treat, the combination of acitretin with cyclosporin was tried, but the cyclosporin had to be discontinued because of rising blood pressure. A trial of combined acitretin and UVB was then planned, as this had been effective in the past for this patient.

The recorded reasons for prescribing acitretin showed that it was selected for patients with extensive or severe psoriasis when the patient was male and when:

- The disease had failed to respond to other systemic treatments
- Other systemic treatments were contra-indicated

PUVA

Six patients were referred for PUVA treatment (5 new course and one in the past). There was one female and five male patients (average PASI 10.0 ± 3.0 (SEM)) In none of the five cases of new treatment was any outcome data available. On four occasions treatment had not started and in the remaining case there was insufficient information in the medical record to show the status of the PUVA treatment.

The recorded reasons for prescribing PUVA showed that PUVA was selected for patients with extensive or severe psoriasis when:

- The response to MTX or CSA was inadequate or complicated by intolerable side effects
- MTX, CSA and ACI were contra-indicated
- Intensive (often in-patient) topical treatment was unsuccessful

UVB

Nineteen patients were referred for 21 courses of UVB treatment (9 female 10 male, average PASI 10.5 ± 1.8 (SEM)). (See Table 12.6) UVB was given in combination with coal tar, with dithranol

and alone, however the details were not clear in the medical records. No records of the actual treatment (doses of UVB, narrow band or broad band etc were made in the main medical record. On eight occasions there was no record of the outcome of treatment (2 referred but not started, 4 did not return to the clinic, 1 referred but did not attend for UVB treatment, 1 referred but suffered a flare up of psoriasis requiring methotrexate treatment before UVB could be started.) UVB treatment was ineffective in one case and treatment was changed to oral cyclosporin. In the remaining 12 cases UVB treatment was judged to be partially or completely successful.

The recorded reasons for prescribing UVB showed that UVB was selected for patients with extensive or severe psoriasis when:

- The disease was predominantly small plaque or guttate psoriasis
- UVB had been effective in the past
- There was some, but insufficient, response to out-patient topical treatment (often involving a combination of coal tar products, steroids, calcipotriol and antifungal agents, in addition to specific scalp products)

Age and PASI

Table 12.7 shows the age and PASI characteristics for each of the treatment groups. In this sample, patients in the groups receiving methotrexate, acitretin and PUVA treatments were older than those in the groups receiving cyclosporin or UVB.
The PASI characteristics also differed. Patients in the group receiving cyclosporin had a mean PASI score approximately twice that of patients in the other treatment groups.

12.3.3 Discussion

It was disappointing to find that such a large proportion of the medical records was missing. Repeated attempts were made to trace the missing records over a period of three months. Originally, it had been assumed that the majority of patients attending the psoriasis speciality clinic would have moderate-severe disease that would require systemic treatment. It was therefore surprising to find that only 48 out of the 166 cases whose records could be traced, fell into this category.

It is clear from the analysis of the psoriasis assessment forms that many patients did not have severe disease according to their PASI scores at the time of assessment. The shortcomings of the PASI

score in this respect are well-recognised (see Chapter 3) and their disease was clearly severe enough by their own assessment and/or their GP's assessment to warrant a specialist referral. The situation may be complicated by the limited facilities for effective management of psoriasis in primary care. Moreover, the time lag between referral and the actual clinic appointment can be several months, during which time the disease has gone into remission, either spontaneously or as a result of successful topical treatment.

The analyses of treatment pathways are therefore based on a small sample and are almost certainly insufficient for quantitative evaluation. Nevertheless, they provide useful insights into the qualitative aspects of treatment that can be built into future models. (See Chapter 13)

The reasons for the choice of systemic treatments followed the accepted, published guidelines. (Gawkrodger 1997).

In this small sample it appeared that cyclosporin, methotrexate and UVB treatments were used more commonly than PUVA. This is likely to reflect two aspects of the local situation. First, there was considerable expertise in the use of cyclosporin and methotrexate in the Dermatology department and second, there was a long waiting list for PUVA treatment. None of the five patients who were referred for PUVA treatment in this sample had received the treatment during the study period. This appears to be a widespread problem and it is of interest that Einarson (Einarson 1994) also noted that shortage of PUVA facilities was an obstacle to its use.

Analysis of the treatment groups by age and PASI score suggests the possibility that different approaches were used in this clinic for different groups of patients. For example, patients in the group receiving cyclosporin were younger than those receiving methotrexate, acitretin or PUVA and had significantly worse disease, according to their PASI scores. This finding is interesting because, in discussions, the consultant dermatologists would stress the importance of using cyclosporin later rather than earlier in order to avoid exposing patients to the risk of renal damage early in life. The low average age may reflect the fact that young patients with very severe disease are preferentially referred to the clinic or may reflect a group of young well-informed patients who demand cyclosporin treatment, or a combination of these factors. UVB was used more frequently than had been expected, although it was difficult to determine consistently from the medical records which patients received UVB alone and which patients received UVB in combination with dithranol or coal tar. Similarly, it was not clear whether narrow band or broad band UVB was in use. The frequency of use of UVB-based treatment, coupled with the fact that the median age of the patients who received it was 26 years, suggests that young patients with severe disease were guided towards this treatment rather than a systemic treatment. A more likely explanation for this observation is that all patients with guttate psoriasis, who tend to be young patients, often with their first episode of psoriasis, were prescribed UVB.

The other important question to be answered by these studies was whether the patterns of treatments observed in this UK sample would be consistent with the decision-analytic model proposed by Einarson (described in Chapter 5). In essence, the model says that if treatment of psoriasis with a given agent ('primary treatment') is successful, then a future episode of psoriasis in the same patient can be treated with the same agent again. If, at any stage, the chosen primary agent is ineffective then it is assumed that a secondary agent will be used. Einarson's study involved four treatments – cyclosporin, methotrexate, etretinate and PUVA. In the model the secondary treatment for methotrexate, etretinate and PUVA was cyclosporin and the secondary treatment for cyclosporin was methotrexate.

The purpose of any model is to codify what happens in reality and this necessarily involves a degree of simplification. The patterns of treatment seen in this sample of patients broadly followed the Einarson model (see Figure 5.1). Where a treatment had been effective in the past it was usually repeated for subsequent episodes. In Einarson's study, the assumptions about secondary treatments, in particular, the definitions of 'success' and 'failure' were not explicit. If 'failure' is defined broadly as either lack of efficacy or manifestation of intolerable side effects, then the model is applicable to the situation in this study. The only remaining problem is the choice of secondary treatment. Einarson's model uses cyclosporin as the secondary agent for the three other treatments, which implicitly assumes that it is usually appropriate. In the present series, methotrexate was chosen as the primary treatment in three cases because cyclosporin was not suitable (by reason of a history of cancer, patient preference or because the patient was considered too young to be exposed to the risks of cyclosporin treatment). Clearly in these situations, cyclosporin would not be a satisfactory secondary treatment, however, if these considerations affect a relatively small proportion of patients then the model is not invalidated.

12.4 Conclusions

Taken together, the results of the assessment forms study and the treatment pathways study suggest that the profile of the group of patients attending the psoriasis speciality clinic broadly conforms to profile of patients with moderate-severe psoriasis who have been recruited to published RCTs. This confirms that is appropriate to combine data drawn from published RCTs with cost data derived from this group, in an economic analysis.

Table 12.2: Treatment pathways for patients receiving methotrexate

Study No	PASI	MTX Rx	Reason for choice of methotrexate treatment	Reason for discontinuation/next treatment
165	12.0	New	Extensive CPP with arthritis. Does not drink alcohol.	LFTs raised. MTX D/C Referred for PUVA
163	10.4	Cont.	Widespread small plaque psoriasis.	Fertility. CSA (MTX restarted after 6 months CSA – wife pregnant)
154	17.1	Cont.	Extensive CPP UVB ineffective; ACI – bad side effects; CCT/dithranol – burns. MTX 'works brilliantly'	
106	17.8	Cont.	Extensive CPP H/o breast cancer	
105	8.5	Cont.	Not recorded	MCV raised MTX D/C Hospitalised
103	3.0	Cont.	CPP + arthritis	
100	13.7	New	Extensive psoriasis, difficult to treat topically	Nausea, bloating, headache & dizziness. MTX D/C Topical treatment
97	3.9	New	Extensive guttate lesions a + large plaques on limbs and buttocks. Patient not keen to take CSA.	Nausea, anorexia, constipation MTX D/C Topical treatment and natural sunlight
80	7.4	Cont.	Extensive small plaque psoriasis. Mucocutaneous SEs with ACI. PMH of non-melanoma skin cancer. MTX well-tolerated	
76	19.3	New	Extensive CPP	Flu MTX D/C MTX restarted
7	11.4	New	Rapidly relapsing psoriasis. CSA not ideal as in view of patient's age. (young)	Jaundice (unrelated to MTX) MTX D/C MTX restarted
8	17.0	New	Severe psoriasis – had responded to Skin-Cap – now discontinued	
9	20	Cont.	Not recorded	
29	5.4	Cont.		No reason recorded MTX D/C Topical treatments

Table 12.3: Treatment pathways for patients receiving cyclosporin

Study No	PASI	CSA Rx	Reason for choice of cyclosporin treatment	Reason for discontinuation/next treatment
163	10.4	New	Restoration of fertility (on MTX)	9/12 treatment. Raised serum creatinine. D/C MTX reinstated .
161	11.4	New	Severe psoriasis	2/12 treatment (clinical trial). Clear. Tingling in fingers and mild headache
		New	Relapse	1/12 treatment. Clear. Tingling in fingers
		New	Relapse	2/12 treatment. Clear.
		New	Relapse	6/52 treatment. Clear.
		New	Relapse	2/12 treatment. Clear. Tingling in fingers
		New	Relapse	
159	3.2	New	Severe scalp psoriasis	2/52 treatment. Nausea +++. D/C. MTX discussed. Topical treatment prescribed.
155	31.9	New	Severe psoriasis, long history.	
151	39.4	New	Severe disease	15/52 treatment. 75% clear. BP 160/118
		New	Mild flare up	
149	28	Cont		
133	36	New	Unstable CPP; erythema ++; alcohol problem	2/12 treatment. Good control. BP 140/95
			Flare up of psoriasis	5/12 treatment. Good control. Swelling of legs - ? due to CSA?
127	25	New	Active psoriasis - failed to respond to MTX	* Also taking acitretin
101	16.3	New	Widespread CPP on face and scalp.	
91	55	New	Erythrodermic psoriasis	
56	20.6	New	Widespread active psoriasis. Inpatient treatment not possible.	
54	11.8	New	Widespread disease, difficult to treat topically; unable to attend for phototherapy	3/12 treatment. Clear
		New	Extensive CPP	
53	15.9	New	Extensive CPP	
57	20.9	New	Widespread CPP	
60	2.7	New	CPP + probable psoriatic arthritis	4/12 treatment. Viral illness
		New		
25	22.7	New	Severe psoriasis	2/12 treatment. BP raised in spite of nifedipine. D/C. Change to acitretin
33	12.8	New	Widespread small plaque psoriasis	2/52 treatment. Did not attend clinic.

Table 12.4: Treatment pathways for patients receiving acitretin

Study No	PASI	Acitretin Rx	Reason for choice of acitretin treatment	Reason for discontinuation/next treatment
128	13.0	New 50mg/d	Mixed plaque & guttate psoriasis; wants inpatient treatment; ACI pro tem.	7/12 treatment. D/C during alcohol detox. Psoriasis still bad – PASI 15.9 – admitted for IPT with dithranol and UVB.
127	25.0	New 50mg/d	H/O treatment with PUVA & ETR. Failed to respond to MTX. Extensive disease – ACI added to CSA	7/12 treatment. D/C when did not attend clinic.
		New	Extensive disease – ACI restarted (CSA continued)	CSA D/C. Plan to add UVB to ACI (effective in past)
91	55	Cont 75mg/d	Erythrodermic psoriasis	D/C - thought to be contributing to erythroderma. Restart CSA (effective in past)
87	0.0	Cont 20/10mg alternate days, then 20mg/d	Totally clear on low dose ACI	Excellent control. Continue ACI.
80	7.4	Cont 20mg/d	Long history of systemic treatment. Non-melanoma skin Ca – no further phototherapy possible. Extensive small plaque psoriasis. ACI + MTX	Continue ACI + MTX
42	8.9	Cont 20mg/d	History of treatment with phototherapy and MTX. Extensive psoriasis. Calcipotriol added	2/12 ACI + calcipotriol. Much improved. D/C ACI. Start again if disease flares.

Table 12.5: Treatment pathways for patients receiving PUVA

Study No	PASI	PUVA	Reason for choice of PUVA treatment	Progress/response
165	12.0	New 2/wk for 12 wks	Little response to MTX; rising ALT	Referred for PUVA but not yet started
119	5.6	New (no details)	Relapse ('scattered large, inflamed plaques + multiple small eruptive spots'). Unsuitable for MTX, CSA or ACI.	Referred for PUVA but not yet started
116	4.1	New	Cannot cope with topical treatment; depressed.	PUVA not started – very limited disease - referred for UVB.
108	3.9	New	Responds well to daily dressings (clinic) with coal tar but less well to home use of coal tar	Referred for PUVA but not yet started
7	11.4	New	Episode of gallstones & jaundice whilst taking MTX. MTX D/Cd	Record does not show whether PUVA started
25	22.7	Past	Side effects with CSA and MTX.	PUVA caused burns

Table 12.6: Treatment pathways for patients receiving UVB

Study No	PASI	UVB	Reason for choice of UVB treatment	Progress/response
153	19.5	New	Inadequate response to topical coal tar and steroids	1/52: Psoriasis improving: UVB continued + coal tar
150	5.7	New	Inadequate response to topical coal tar, steroids & calcipotriol scalp lotion.	2/52: Psoriasis improving: UVB continued + topical steroid
143	11.1	New	Extensive small plaque psoriasis + palmo-plantar pustular psoriasis. Patient is reluctant to use systemic treatment. Plan: dithranol +UVB as in-patient	Improved with UVB and daily dressings. UVB D/Cd.
			Flare-up due to job stress. UVB and topical treatments restarted.	Did not attend clinic – no record of UVB tx.
135	5.0	New 2/wk for 8 wks	Inadequate response to topical coal tar, steroids & clotrimazole	Improved with UVB but flared when patient had exams. Did not return to clinic
130	10.0	New 24 sessions	Inadequate response to topical dithranol. UVB effective in past.	4/12 treatment. 'UVB not really helping – PASI 15.3. Plan for CSA.
122	14.3	New	Extensive CPP. UVB effective in past.	2/12 >90% clear on UVB + betamethasone ointment 1 in 4.
116	4.1	New	Cannot cope with topical treatment; depressed.	Referred for UVB but did not attend
109	6.7	New 2/wk for 8 wks	Inadequate response to topical dithranol, steroids and salicylic acid. UVB effective in past.	Course completed. Good control.
97	3.9	New 2/wk for 8 wks	Inadequate response to calcipotriol and topical steroids.	Topical coal tar and salicylic acid prescribed – caused flare before UVB started - MTX Rxd. UVB not given
96	15.9	New	Small plaque/guttate psoriasis	Referred for UVB but not yet started
95	9.0	New 3/wk	Extensive plaque psoriasis. Good response to tacalcitol, Add UVB	30 sessions completed. Partial improvement (Topical treatments not used)

Table 12.6: Treatment pathways for patients receiving UVB (continued)

Study No	PASI	UVB	Reason for choice of UVB treatment	Progress/response
94	16.2	New 2/wk for 12 wks	Widespread thin plaques	Course completed: > 90% clear. Topical treatment – calcipotriol, steroids, coal tar and anti-fungal cream ran out!) Continue with topical tx.
		New	Flare of guttate psoriasis on trunk and limbs. UVB effective in past.	2/12 Good progress.
93	3.8 (excludes trunk)	New For 3 wks	Thin, small plaques on limbs + guttate lesions	Did not attend clinic – no record of UVB tx.
89	9.8	New	Very active small plaque psoriasis	Did not attend clinic – no record of UVB tx.
85	17.1	New	Extensive annular CPP over trunk, limbs and scalp.	Did not attend clinic – no record of UVB tx.
66	6.4	New 3/wk	Scattered guttate and plaque psoriasis	10/52: UVB + topical calcipotriol and Daktacort. 19 sessions: 95% improvement. Pt discharged
65	32.8	New 2/wk	Thick inflamed plaques on legs, arms and trunk. Good response to topical treatment with coal tar/salicylic acid and steroids. Add UVB	20 treatments given: patient 'very pleased with results of UVB'. Pt discharged
27	5.4	New	Psoriasis mainly on lower limbs. Inadequate response to topical coal tar and steroids	Referred for UVB but not yet started
49	3.0	New 3/wk for 20 wks	Moderately thick and scaly plaques – 4% BSA	12 sessions: improving

Table 12.7: Summary of characteristics (age and PASI) for each treatment group

	MTX 14 patients	**CSA 17 patients**	**ACI 6 patients**	**PUVA 6 patients**	**UVB 20 patients**
Age ± SEM (years)	47.7 ± 3.4	33.6 ± 3.5	50.3 ± 7.4	49.5 ± 7.0	33.4 ± 4.3
Median age (years)	44.5	31	48	46	26
PASI ± SEM	11.9 ± 1.5	21.4 ± 3.3	10.0 ± 3.5	10.0 ± 3.0	10.5 ± 1.8

Chapter 13

Economic analysis of treatments for severe psoriasis

Summary

The procedure adopted for application of the previously published decision analytic model are described, including the assumptions made, and the identification of treatment success and relapse probabilities. The analyses performed provide a rank order for the treatment strategies considered and give additional insights into the relative cost-effectiveness of the four strategies. The potential sources of variation are identified and recommendations for future analyses are made

13.1 Introduction and background

A critique of previous analyses of psoriasis treatment has already been presented in Chapter 4.

The original plan for this project was to repeat the analysis described by Einarson and colleagues (Einarson 1994) using information derived from the systematic reviews described in Chapters 7-10 and current UK cost data to populate the decision analytic model. However, close examination of Einarson's report revealed a number issues that required clarification before further application of the model. (These were discussed in detail in Chapter 5.) In particular, clarification was needed concerning

- Whether treatments were continuous or intermittent
- Dosage and duration of treatment
- Relapse rates
- Time frame for the model

Continuous or intermittent treatment

In line with current treatment recommendations, the model should incorporate continuous treatment with methotrexate and acitretin, but intermittent treatment with cyclosporin and PUVA. (Gawkrodger 1997)

Dosage and duration of treatments

In general, the doses used in the model should reflect the doses used in the trials on which the estimates of effect size are based. For cyclosporin and acitretin these are 3-5 mg/kg/day and 0.5-0.75 mg/kg/day. For methotrexate there were no RCTs on which to base estimates of effect size and so cohort studies were used to derive a response rate (see table 13.3) and the dose was taken from current guidelines (Gawkrodger 1997). For PUVA a course of 20 sessions is assumed as this is commonly prescribed in practice and in the trial situation. The duration of treatment should represent the time in which the majority of patients could be expected to have responded. For all treatments this was assumed to be 8-12 weeks.

Relapse rates and time frame

One of the important elements of the model is the anticipated times to relapse after treatment. Patients with psoriasis are at a continuous risk of recurrence (relapse) but, in order to embrace this in the framework of a decision analytic model, the probabilities of relapse at specified time intervals need to be incorporated.

A previous history of severe or 'resistant' psoriasis is believed to be a major factor influencing relapse rates, (Higgins 1989) and for this reason the same relapse rate was used for all treatments in the model. Published studies show that, for many patients, relapse occurs within three months of discontinuation of treatment. For example, the multi-centre study of intermittent cyclosporin use reported by Ho and colleagues (Ho 1999) showed that the median time to relapse after abrupt discontinuation of cyclosporin was 109 days. In this one-year study patients were allowed to have as many course of cyclosporin as were required. The numbers of patients who required one, two three and four courses of treatment were 400, 259, 117 and 26,respectively. For the purposes of the model a relapse rate of 0.35 at twelve weeks after discontinuation of treatment was used. This corresponds to the observed rate in the study by Ho and colleagues (Ho 1999). The 'on-treatment' relapse rate for patients receiving maintenance treatment with methotrexate or acitretin was arbitrarily set at 0.1 at twelve weeks after initial clearance.

Time frame for decision analytic model

If twelve-week treatment periods and twelve-week 'relapse evaluation' periods are incorporated into Einarson's decision analytic model, as shown in figure 13.1, then the model covers a period of approximately one year (48 weeks).

13.2 Data sources

The data required to populate the decision analytic model are treatment success rates (at 12 weeks), relapse rates at 24 weeks (i.e. 12 weeks after discontinuation of PUVA or CSA, 24 weeks after starting acitretin or methotrexate), and the costs of treatment.

13.2.1. Success rates

The success rates for cyclosporin, acitretin and PUVA treatments were calculated by a weighted pooling of the success rates (on an 'intention to treat' basis) of the appropriate RCTs identified in the systematic review (see tables 13.1, 132, 13.4). RCTs using ineffective doses or out-dated dosage regimens were excluded. Thus, for cyclosporin, only trials using doses of 3 mg/kg/day or above were included and the single study that used a dose of 14 mg/kg/day was excluded. The success rate for methotrexate was taken from two open trials (see table 13.3).

Confidence intervals for success rates were calculated according to the method for determination of the confidence interval for a binomial population parameter described by Altman (Altman 1991) and implemented using Intercooled Stata 6.0 for Windows (Stata Corporation, Texas)

Primary treatment success rate (average success rates; 95% CI))

CSA	0.70 (95% CI 0.67 – 0.73)
MTX	0.61 (95% CI 0.51 – 0.71)
ACI	0.45 (95% CI 0.38 – 0.52)
PUVA	0.79 (95% CI 0.77 – 0.82)

Table 13.1: Cyclosporin success rates

Cyclosporin response rate (all series, dose > 2.5 mg/kg/day			
Author/year	Number of successes	Number in group	Comparator
Van Joost 88	7	10	plo
Engst 89	3	6	plo
Ellis 91a	9	25	plo
Ellis 91b	13	20	plo
Ellis 91c	12	15	plo
Guenther 91	11	12	plo
Meffert 95	12	44	plo
Finzi 93	35	36	etr
CSCG 91	40	79	bet
Christophers 92a	60	121	csa
Christophers 92b	41	60	csa
Laburte 94	117	132	csa
Elder 95 neo	16	18	csa-sim
Elder 95 sim	16	19	csa-neo
Koo 95 neo	122	152	csa-sim
Koo 95 sim	122	156	csa-neo

Cyclosporin average success rate 0.70 (95% CI 0.67 – 0.73)

Table 13.2: Acitretin success rates

Success rates - Acitretin doses 50mg/day, 0.75mg/kg or greater			
Author/year	Number of successes	Number in group	Comparator
Goldfarb 88c	2	11	plo
Lassus 87c	14	20	plo
Gollnick 88c	9	43	etr
Bauer 83	29	71	etr
Finzi 93	29	40	csa

Acitretin average success rate 0.45 (95% CI 0.38 – 0.52)

Table 13.3: Methotrexate success rates

Success rates - Methotrexate		
Author/year	Number of successes	Number in group
Nyfors 70	41	50
Weinstein 71	20	50

Methotrexate average success rate 0.61 (95% CI 0.51 – 0.71)

Table 13.4: PUVA success rates

PUVA response rates (all series)		
Author/year	Number of successes	Number in group
Andrew 81	24	26
Berg 94	24	38
Buckley 95	72	83
Collins 96	61	74
Lowe 87	32	47
Tanew 88	166	169
Collins 92	28	44
Turjanmaa 85	79	93
Pai 94	9	12
Williams 85	2	4
De Berker 97	37	50
Rogers/VB 79	103	113
Lauharanta 81	16	20
Parker 84	9	15
Sommerburg	19	44
Tanew 91	20	30
Frappaz 93	29	53

PUVA average success rate 0.79 (95% CI 0.77 – 0.82)

13.2.2 Costs

Resource inputs comprised staff time, laboratory investigations, clinic visits, treatment costs (PUVA treatment or costs of medicines and dispensing).

Staff time

Staff time (doctors, nurses, phlebotomist, receptionists, medical records and pharmacy staff) along with clinic overheads (heating, lighting, capital charges) are all embraced in the out-patient attendance cost of £76.00. (source: Finance Department at Hope Hospital) Although originally observational studies had been performed to determine the amounts of time spent by clinical staff (doctors, nurses, phlebotomists) it had not been possible to capture accurately the time spent by secretarial staff and medical records staff. After discussion with the Deputy Director of Finance, it was decided that the aggregate figure would provide the more accurate data.

Laboratory costs

The costs of routine laboratory tests are covered in the out-patient attendance cost but non-routine items, such as X-rays or invasive procedures are not and were therefore costed separately. The costs of relevant laboratory tests were taken from current (2001) hospital costs. (See Table 13.6)

Table 13.6: Costs of laboratory tests and investigations

Test	Cost (£)
Biochemical profile	8.08
Urea, electrolytes & creatinine	2.96
Lipid profile	5.85
PIIINP*	8.00
Glomerular filtration rate*	8.00
Full blood count	1.89
Pregnancy test	6.17
X-ray spine	106.00
Liver biopsy	650.00

(Source: Finance department Hope Hospital, Salford. * exact prices not available, tests charged at average rate.)

Drug costs

The costs of the drugs used was taken from the British National Formulary number 42 (October 2001) except for 8-methoxypsoralen (8-MOP). 8-MOP is unlicensed in the UK and the price was obtained from the manufacturer.

Table 13.7 Drug costs

Drug	Strength	Pack size	Price (£)	Unit price (£)	Dose	Cost/12wks treatment
Methotrexate	2.5	100	11.41	0.114	15mg/wk	8.22
Methotrexate	10	100	55.07	0.551	20mg/wk	13.22
Neoral (CSA)	100	30	76.33	2.544	400mg/d	854.90
Neoral (CSA)	100	30	76.33	2.544	300mg/d	641.17
Acitretin	10	56	25.34	0.453	35mg/d	126.21
Acitretin	25	56	58.8	1.05	50mg/d	176.40
8-MOP	10	100	34.00	0.34	40mg	27.20*
8-MOP	20	50	50.00	1.00	40mg	40.00*
Folic acid	5	20	0.49	0.025		2.06

*assumes 20 PUVA treatment sessions

PUVA costs

PUVA costs were based on the number of out-patient attendances. For the purposes of this analysis it was assumed that each patient would receive twenty treatments and that the cost of each treatment session was £76.00.

13.3 Analysis

Einarson's model was redrawn using the conventional notation and substituting 'clearance' or 'no clearance' for success and failure. (Figure 13.2) The final outcomes are also shown as 'clearance' or 'no clearance', rather than 'success' or 're-evaluate' as in the original. These terms are more helpful and are genuine outcomes, whereas, for example, 're-evaluate' is not an outcome, as such, but an action to be taken in the event of an unsatisfactory outcome.

Spreadsheets were constructed as described in Chapter 5 to determine the cumulative probabilities of clearance/no clearance with each of the treatment strategies. Costs were then incorporated into the model in order to calculate the cost of each strategy. A cost-effectiveness ratio was calculated by dividing the cost by the overall success rate to give a 'cost per cleared case'.

As an example, table 13.8 shows the calculations for the strategy that uses cyclosporin first and methotrexate as a back up treatment.

A number of assumptions are made in using the model and it is important that they be recognised:

- All patients receive the full course of treatment
- All patients are carefully monitored and severe adverse effects (requiring discontinuation of treatment) of treatment are avoided.

Table 13.9 shows the average probabilities of clearance with each of the four strategies and the 'base case' cost-effectiveness ratios

13.3.1 Sensitivity analyses

Once the base-case cost-effectiveness (CE) ratio had been calculated for each of the treatment strategies, then the effects of varying key assumptions were tested. The results are shown in table 13.10. Decreasing the relapse rate had a modest effect on all the CE ratios. Varying the success rate of the primary treatment between the calculated confidence limits had modest effects on the treatment strategies that used cyclosporin or PUVA as the primary treatments but more marked effects on those that used methotrexate or acitretin. In both these cases the calculated confidence intervals were relatively wide and the corresponding CE ratios differed considerably from the base case, but the overall ranking did not change

Attendance at the outpatient clinic attracts a cost of £76.00. The base case assumes that all patients attend the clinic once a month. The effect of reducing the frequency to once every three months was examined but it had little effect on the overall CE ratio. Furthermore, it is doubtful that patients taking methotrexate or cyclosporin could be adequately monitored in this situation.

The base case analyses show that the strategy using methotrexate as the primary treatment delivers a considerably lower CE ratio than any of the other three strategies. It should be noted however, that this analysis excludes the cost of a liver biopsy. If this is incorporated into the pathways that include twelve months' treatment with methotrexate then the CE ratio rises to 2042, which still compares favourably with the cyclosporin-methotrexate strategy.

None of the substitutions used for sensitivity analyses changed the rank order of the treatment strategies.

13.4 Discussion

The use of the cost-effectiveness ratio – the cost per cleared case – provides a way of taking account of the fact that the different treatment strategies result in different outcomes. Although each of the chosen strategies can lead to clearance of psoriasis, the probabilities of a successful outcome vary between 77% and 90% (see table 13.9). It is therefore not appropriate simply to compare the costs of each strategy, as in a cost-minimisation analysis. A cost-effectiveness analysis, which incorporates a natural measure of outcome, in this case clearance of psoriasis, is the appropriate method to provide a meaningful comparison.

Methotrexate given as the primary treatment with cyclosporin as the secondary treatment appears to be the most cost-effective option, however, further analyses would be necessary before this could be recommended as a routine treatment policy. As noted above, if an annual liver biopsy is required (Gawkrodger 1997) then the expected cost of treatment approaches that of the cyclosporin-methotrexate strategy. Furthermore, the costs of the cyclosporin-methotrexate strategy may be over-estimated, because a dose of 5mg/kg/day was assumed, whereas in one large trial that used intermittent treatment with cyclosporin, the average dose used did not exceed 4mg/kg (Ho 1999). However, reducing the dose of cyclosporin in the model to 300 mg/d only reduces the CE ratio to 2025. In addition, the effectiveness of the strategy may be under-estimated because the analysis was based on doses of cyclosporin ranging from 2.5 - 7.5 mg/kg/day. If doses below 3mg/kg/day are excluded then the success rate improves.

The PUVA-cyclosporin strategy is the least cost-effective in this analysis, and this is clearly related to the expense of hospital attendance.

In view of recent developments an additional treatment strategy needs to be added to this comparison. The observational study showed that UVB treatment was in regular use although it was not clear what proportion of this was narrowband UVB and what was therapy with the Ingram regimen. Given the growing popularity of narrowband UVB as a single therapy, it would be appropriate now to build in an arm to examine effects of this treatment.

Perhaps the most fundamental issue to address is whether the model itself is appropriate. The purpose of a decision–analytic model is to represent all the possible pathways and outcomes in a given situation. Although Einarson's model satisfies this requirement in some respects, in others it does not. For example, no time frame was given in the original description and this is important for a meaningful analysis. If it is assumed that the model spans a one-year period then there may need

to be an allowance for another repeat treatment with the primary treatment. In the original model, patients following pathway number 1 achieve clearance in the first treatment period and have no relapse for next nine months. In the study by Ho and colleagues (Ho 1999) more than 25% of the participants required a third course of treatment within a one-year period. This is a large enough proportion to merit inclusion in the model. This is further indirectly reinforced by the results of the observational study, which showed that on many occasions, a treatment was selected because it had worked in the past. One way of incorporating these two elements would be to construct branches of the decision tree that reflect these possibilities. If pathways were also included that allowed treatment to be changed at any stage, for example if side effects became intolerable, then a more accurate representation of the real situation may be possible. Figure 13.3 shows how this could be done for the cyclosporin branch.

Another important aspect of the model is that it makes no allowance for the adverse effects of treatment. It is assumed that monthly clinic visits are made and that all the appropriate monitoring and dosage adjustments are carried out, and in this way adverse events are avoided. This approach has been used by Davies and colleagues (Davies 1997), but their analysis was concerned with short course cyclosporin for mild-moderate psoriasis, where the assumption may have been more easily justified. In the present study, concerned with moderate-severe disease, rare but costly adverse events could alter the conclusions of the analysis considerably. Ideally, data for this should be taken from long-term follow-up studies, in the real-life situation, and be built into the model.

Both the original model and the modifications proposed above assume that relapses occur three months after the end of treatment to induce remission of psoriasis. In real life, patients are at continuous risk of relapse and some will relapse earlier than three months, but others will not relapse until much later. One way of taking account of this type of dynamic process is through the use of Markov modelling. A Markov model is essentially a much more complex decision tree that shows all the possible health states that a patient could be in at a pre-determined point in time (Drummond 1997). Thus for patients one month after successful treatment with cyclosporin, possible health states are cleared and receiving no treatment, relapsed and receiving no treatment, relapsed and receiving re-treatment with cyclosporin. In order to analyse a Markov model the length of the Markov cycle has to be determined (how often patients would be evaluated) and the transition probabilities (the rate at which patients will move from one health state to another) need to be calculated. Perhaps the most serious limitation of a Markov model is that it assumes 'zero memory', that is, the transition probabilities depend only on the health state a patient is in and not on how long they have been there or how they got there. In the case of psoriasis, where a previous history of severe or 'resistant' disease is believed to be a major factor influencing relapse rates, (Higgins 1989) this assumption could not possibly hold.

A useful alternative approach to all of these issues would be to use a consensus panel of dermatologists to determine the treatment pathways to be incorporated into the model. This would confer a degree of validity that can never be achieved by the theoretical approach alone.
This analysis has been performed from the perspective of the health service and is concerned with costs and effectiveness, which has been defined largely by clinicians. The results of the clinical trials on which the analyses are based are predominantly physicians' assessments of responses to treatment. Another useful perspective could be gained by performing a cost-utility analysis for the four treatment strategies. This would involve first determining patients' preferences for the difference types of treatment. A previous study concerned with economic analyses of methotrexate versus Goeckerman therapy for psoriasis reported a trend towards a greater cost-effectiveness when patient utilities rather than physician utilities were used (Chen 1998).

13.5 Conclusions and recommendations

This preliminary economic analysis using a previously-published decision-analytic model has provided a rank order of cost-effectiveness for the four treatment strategies compared and has raised a number of issues about the model itself.

The analyses that have been performed provide some insights into the relative costs and effectiveness of the treatment of moderate-severe psoriasis however, before these could be used for policy decisions, a more detailed model is required. Such a model would need to be tested out with expert dermatologists to ensure that it reflected current approaches to treatment. In particular, more detail about monitoring and follow-up is required. For example, the effects of having some monitoring done by the GP could be explored.

The frequency of unpredictable adverse effects of psoriasis treatments should be determined, if possible, in the real-life situation rather than from clinical trial data.

The use of narrowband UVB should be incorporated into future analyses.

Figure 13.1: The decision-analytic model incorporating time periods for treatment and relapse. (Based on the model proposed by Einarson and colleagues (Einarson 1994))

KEY: PSR – primary treatment success rate; PRR – primary treatment relapse rate; SSR – secondary treatment success rate; SRR – secondary treatment relapse rate; PRSR – primary retreatment success rate

Figure 13.2: Einarson's model redrawn using the conventional notation

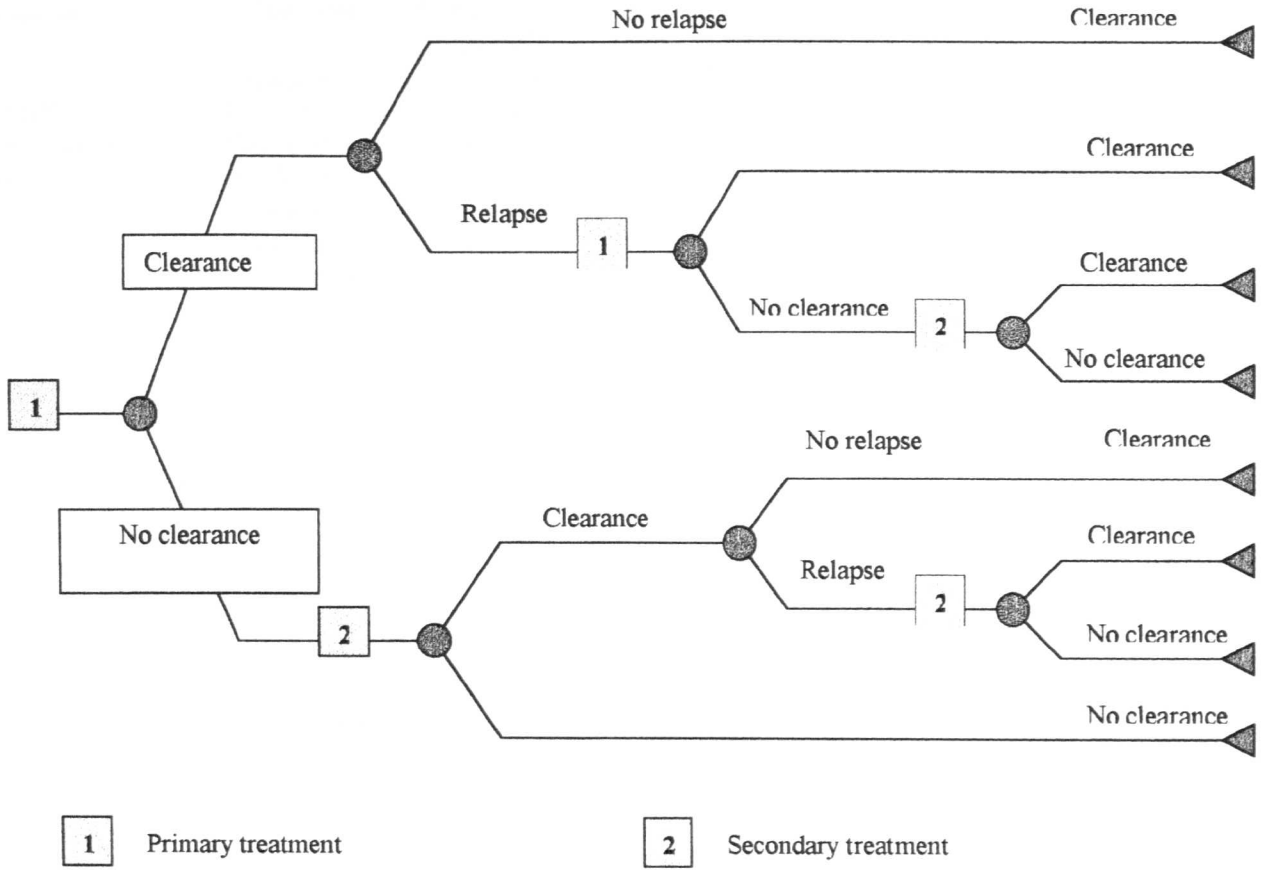


Table 13.8: Costs of using cyclosporin as the primary treatment and methotrexate as secondary treatment

Primary treatment cyclosporin, secondary treatment methotrexate

Description	Outcome	Cumulative probability	Treatment cost	Cost of pathway
Total success	Clearance	0.455	1767	803.985
success,relapse,success	Clearance	0.1715	2622	449.673
success,relapse,failure,success	Clearance	0.044835	2632	118.00572
success,relapse,failure,failure	No clearance	0.028665	2632	75.44628
failure,success	Clearance	0.1647	1777	292.6719
failure,success,relapse,success	Clearance	0.011163	1787	19.948281
failure,success,relapse,failure	No clearance	0.007137	1787	12.753819
Total failure	No clearance	0.117	1777	207.909

Overall success rate	0.847198	Total cost	1980.393
Overall failure rate	0.152802	C/E ratio	2337.579881

(See Appendix 3 for details of calculations)

Notes:

Assumes:

- Monthly clinic attendance for follow up and monitoring.
- Cyclosporin dose 400mg/day; methotrexate 15mg weekly for first treatment period and 20mg weekly for second treatment period.

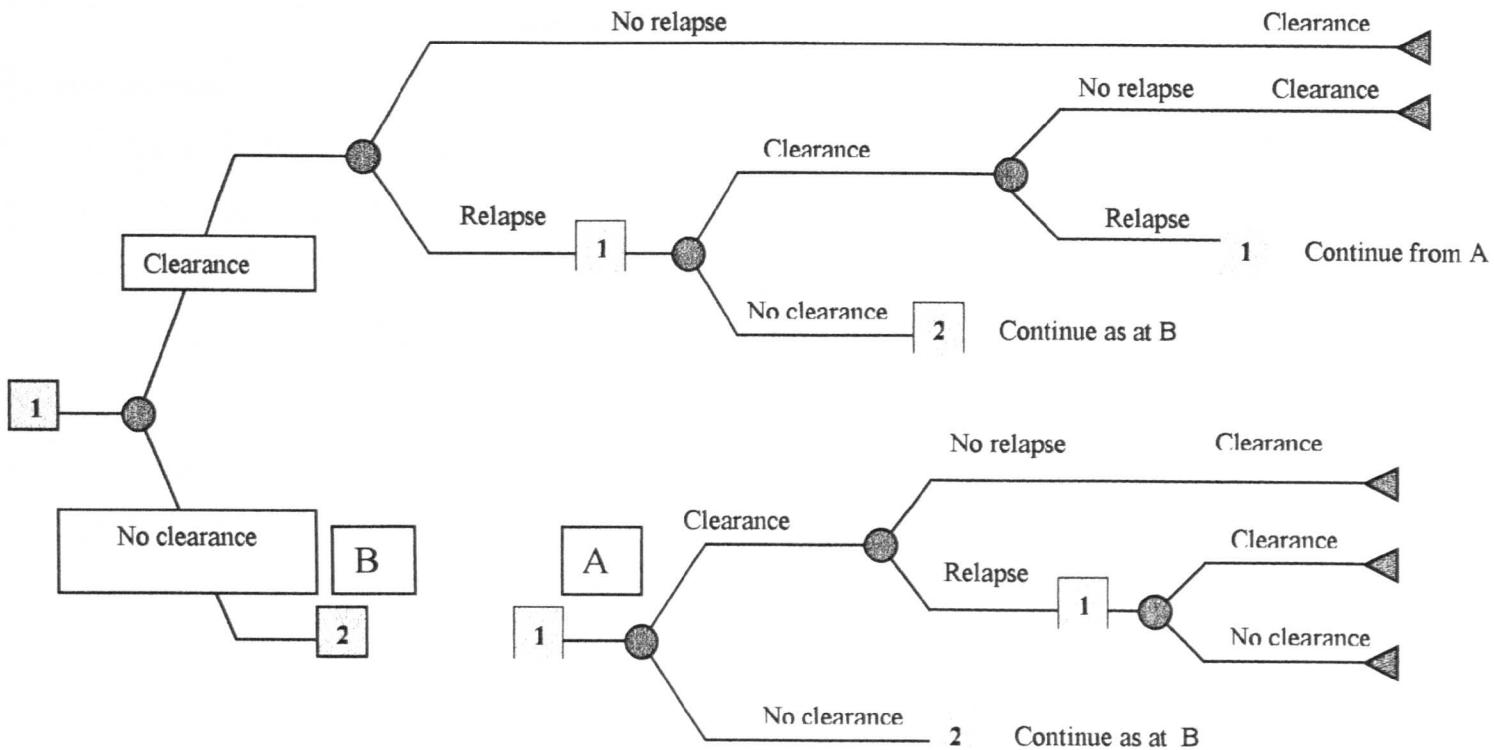
Table 13.9: Average probabilities of clearance with each of the four strategies and the 'base case' cost-effectiveness ratios.

Treatment strategy **Primary treatment; secondary treatment**	**Average success rate**	**Base case C/E ratio** **(£ per case cleared)**
Cyclosporin; methotrexate	0.83	2337
Methotrexate; cyclosporin	0.83	1626
Acitretin; cyclosporin	0.77	2589
PUVA; cyclosporin	0.90	3554

Table 13.10: Sensitivity analyses

Treatment strategy Primary treatment; secondary treatment	**Base case C/E ratio (£ per case cleared)**	**Effect of increasing relapse rate to 50%**	**Effect decreasing response rate to primary treatment to lower limit of confidence interval**	**Effect of increasing response rate to primary treatment to upper limit of confidence interval**
Cyclosporin; methotrexate	2337	2569	2365	2309
Methotrexate; cyclosporin	1626	1849	1941	1417
Acitretin; cyclosporin	2589	2871	2724	2461
PUVA; cyclosporin	3554	3811	3641	3496

Figure 13.3: Proposed treatment branch for cyclosporin



1 Primary treatment - in this case cyclosporin

2 Secondary treatment: another treatment branch would need to be drawn to represent the pathways under the secondary treatment

Table 13.11: Treatment pathways in proposed cyclosporin branch

Pathway number	Sequence of events	Outcome
1	CSA, clear, no relapse	Clearance
2	CSA, clear, relapse, CSA, clear, no relapse	Clearance
3	CSA, clear, relapse, CSA, clear, relapse, CSA, clear, no relapse	Clearance
4	CSA, clear, relapse, CSA, clear, relapse, CSA, clear, relapse, CSA, clear	Clearance
5	CSA, clear, relapse, CSA, clear, relapse, CSA, clear, relapse, CSA, not clear	No clearance
6	CSA, clear, relapse, CSA, clear, relapse, CSA, not clear, ST	Secondary treatment
7	CSA, clear, relapse, CSA, not clear, ST	Secondary treatment
8	CSA, not clear, ST	Secondary treatment

CSA = cyclosporin treatment for 12 weeks
ST = secondary treatment

Chapter 14

Discussion and Overall Conclusions

Psoriasis is a common disease that affects up to 2% of the population of the UK. Although severe psoriasis accounts for only about a quarter of cases – those that are treated in secondary care – the prevalence of moderate-to-severe psoriasis is still equivalent to the prevalence of rheumatoid arthritis or diabetes mellitus. Both of these conditions are perceived as common, disabling and worthy of research efforts. The high prevalence of psoriasis, coupled with its chronic, recalcitrant nature and consequent severe psychosocial disabling effects, mean that it should be no less prominent.

A working knowledge of the effectiveness and tolerability of the treatments available for severe psoriasis, based on firm evidence, is essential for decision-makers in the NHS. Sources of evidence include systematic reviews of RCTs, observational studies of the real-life situation and modelled data. These techniques offer different insights into the effectiveness and utility of treatment strategies. Together they can help health care decision-makers, individual clinicians and patients to select treatments that represent an acceptable balance of clinical effectiveness, utility and cost.

The studies reported here – a systematic review of the effectiveness of treatments for severe psoriasis and a preliminary cost-effectiveness analysis of four treatment strategies – have recorded and synthesised the available evidence. The trials reviewed cover the period up to June 1999. Further work is required to bring the database up-to-date with recently-published trials, and to examine the tolerability of the treatments in more detail and to improve the economic analysis.

The main body of this project was concerned with a systematic review of RCTs of psoriasis treatments. In this area a number of difficulties were encountered, notably the lack of a universally accepted definition of severe psoriasis, the low power of many trials and the standards of reporting. Severe psoriasis can usually be defined as psoriasis involving body surface area >20% and/or a psoriasis area severity index (PASI) of $\geq$12, however this was not applied in all the trials included in the review. Moreover, the PASI reflects clinical severity and not the important dimension of psychosocial disability. Although this could be said of many clinical measurement scales, a special case can be made for skin diseases where psychosocial disability is an important element of the impact of the disease. Low-powered studies *per se* need not necessarily be a problem, particularly if a meta-analysis is possible. However, a large number of trials included in the review had very small numbers of participants (many had 30 or fewer in each group) and therefore gave rise to results with very wide confidence intervals. Some reports of RCTs were insufficiently detailed to allow their inclusion in the review. In addition, the results of some trials were described on a per protocol basis

and others on an intention to treat (ITT) basis. This can have a major impact on the apparent effectiveness of a treatment. Schiffner and colleagues (Schiffner 2001) recently described "striking differences in the therapeutic effect" of treatments for psoriasis and eczema according to the method of analysis that was used. For the purposes of this review all results that were extracted were corrected to reflect the ITT sample. Previous authors have called for improvements in the quality of trial reporting in the dermatological literature (Adetugbo 2000) and the experience of this review suggests that this is justified.

In the reviews of treatments, effect sizes have been presented as odds ratios and risk (rate) differences. The odds ratio is the preferred tool of statisticians and epidemiologists. It is used because of its mathematical properties and because many of the standard meta-analytical methods rely on the use of the odds ratio. However, as Wiffen has observed (Wiffen 2001), "few people have a natural ability to interpret event ratios that are reported in terms of odds ratios." For this reason the results presented in Chapters 7-10 have been recalculated to give the 'number needed to treat' (NNT) in Chapter 11. The most striking feature of the NNTs is their small values, indicating the marked effectiveness of the treatments. No previously published NNTs for psoriasis treatments were located during the preparation of these reviews.

The two observational studies described in Chapter 12 provided real-life data that validated some of the assumptions made in the decision-analytic model that formed the basis of the economic evaluation. One interesting feature to emerge from these studies was the fact that the patients receiving UVB and cyclosporin treatments were younger than those receiving the other forms of treatment. The patients receiving cyclosporin also had higher mean PASIs, suggesting that they may be a subgroup of young patients with particularly severe disease.

The preliminary economic analysis reported in Chapter 13 provided a rank order of cost-effectiveness for the four treatment strategies compared but raised a number of issues about the model itself. According to the analysis, the primary treatments, in order of cost-effectiveness, would be methotrexate, cyclosporin, acitretin and PUVA. In practical terms, acitretin can only really be considered for men and post-menopausal women, because of the risks of teratogenicity. The absence of narrowband UVB from the analysis is a major omission in the present day treatment setting and this should be incorporated into future analyses.

A detailed consideration of the evidence of effectiveness of treatments is the logical starting point for the formulation of treatment guidelines. Both Einarson and colleagues (Einarson 1994) and Spuls and colleagues (Spuls 1998) have made recommendations for treatment guidelines. According to Einarson's analysis, the primary treatments, in order of cost-effectiveness were cyclosporin, etretinate, methotrexate and PUVA. It should be noted that Einarson's team used a cyclosporin dose of 5mg/kg/day for six weeks, whereas the present study allowed for 12 weeks treatment (on the basis of trials that show a full response takes from 8-12 weeks to develop). Spuls and colleagues

developed and tested a set of guidelines based on their earlier systematic review. Taking into account efficacy, safety and tolerability they recommended that treatment should follow the sequence: UVB, PUVA, methotrexate, acitretin, cyclosporin. A flowchart was constructed to guide the choice of treatment and it was designed in such a way as to prompt rotation of treatments. No information is given about the relative costs of the treatments. The authors comment that quantitative measures of patients' preferences should be further investigated. It would be useful to combine the treatment flow chart with UK cost data to examine the economic effects of this scheme and to compare the options that it generates with the model used in the present study.

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

Interventions for which RCT evidence of efficacy can be demonstrated are:

- Cyclosporin
- Systemic retinoids (acitretin and etretinate) particularly in combination with PUVA
- Phototherapy and photochemotherapy: – PUVA, BBUVB and NBUVB
- Combinations of topical calcipotriol and steroids with phototherapy

Interventions for which firm RCT evidence of efficacy is lacking

- Methotrexate

Research recommendations

In view of the lack of RCT evidence in several areas the following trials are recommended:

- A comparison of cyclosporin with methotrexate.
- Comparisons of systemic therapy/phototherapy with inpatients and/or day treatment.
- Comparison of acitretin with methotrexate for long-term treatment.
- A comparison of NBUVB versus PUVA for both short term efficacy and long term safety.

Further studies of the cost-effectiveness and cost-utility of treatments for severe psoriasis are required. Future models will need to incorporate the costs of adverse effects of treatment. Economic evaluations should consider not only systemic and phototherapy options but also inpatient

or day treatment centre management of psoriasis. In addition, combination therapies should be built into future models, so that the real life situation is more accurately reflected.

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Glossary

APCs	Antigen presenting cells
BBUVB	Broad band UVB (290-320 nm)
BSA	Body surface area
CI	Confidence iinterval
CSA	Cyclosporin A
DB	Double blind
Goeckerman therapy	A form of treatment for psoriasis involving the use of UVB and tar
Ingram therapy	A form of treatment for psoriasis involving the use of UVB, tar and dithranol
J	Joule
MED	Minimum erythematous dose (a measure used for UVB)
MOP	Methoxypsoralen
MPD	Minimum phototoxic dose (a measure used for UVA)
NB	Not blinded
NBUVB	Narrow band UVB (approx. 311 nm)
NR	Not reported
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PNBUVB	Psoralen plus narrowband UVB
PSI	Psoriasis severity index (a modified PASI)
PUVA	Psoralen plus UVA
RCT	Randomised controlled trial
RD	Rate difference (also known as risk difference)
RePUVA	The combination of a retinoid with PUVA treatment
SAPASI	Self-administered psoriasis area and severity score
SB	Single blind
SD	Standard deviation
SEM	Standard error of the mean
TMP	Trimethoxypsoralen

UVA	Ultraviolet A (320 – 400 nm)
UVB	Ultraviolet B (290 – 320 nm)
VAS	Visual analogue scale
WTP	Willingness to pay

Appendix 1

Medline Search Strategy to Identify Randomised Controlled Trials

The search strategy below will detect a high proportion of studies which are randomised controlled trials, but may also retrieve some non-randomised studies. The search is in three sections and the sections trade-off recall and precision with the first search (#10) having high precision and lowest recall and the third search having high recall and low precision. The final search line (#31) combines all three searches, but it is also possible to just combine #30 and #10 for high precision if desired.

#1	randomized controlled trial.pt.
#2	randomized controlled trials.sh.
#3	random allocation.sh.
#4	double blind method.sh.
#5	single blind method.sh.
#6	1 or 2 or 3 or 4 or 5
#7	animal.sh.
#8	human.sh.
#9	7 not (7 and 8)
#10	6 not 9
#11	clinical trial.pt.
#12	exp clinical trials.sh.
#13	(clin$ adj3 trial$).ti,ab.
#14	((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
#15	placebos.sh.
#16	placebo$.ti,ab.
#17	random.ti,ab.
#18	research design.sh.
#19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
#20	19 not 9
#21	20 not 10
#22	comparative study.sh.
#23	exp evaluation studies.sh.
#24	follow-up studies.sh.
#25	prospective studies.sh.
#26	(control$ or prospective or volunteer$).ti,ab.
#27	21 or 22 or 23 or 24 or 25
#28	26 not 9
#29	28 not (10 or 21)
#30	****subject search terms****
#31	30 and (10 or 21 or 29)

This is a translation of the search suggested by Dickersin, Scherer and Lefebvre, in *the British Medical Joumal* 1994; **309:** 1291 (NHS CRD 1996)

Appendix 2

Data Extraction Sheet for a Review of Volume and Quality of CABG Surgery

Paper Reference Number

A DETAILS OF PUBLICATION

1 Author

2 Title

3 Reference

4 Institution

B SOURCE OF DATA

1 Where was the data from?

2 What years was the data collected for?

3 How was the data obtained (eg discharge abstracts, database)?

C HOSPITALS AND PATIENTS INCLUDED IN THE REVIEW

1 Did the patients undergo CABG surgery?

2 What cut-points for hospital volume can be used from the paper?

3 What cut point is closed to 200?

4 Number of hospitals above this cutpoint?

5 Number of hospital below this cut-point?

6 What mortality rate(s) does the paper report? (over what period)

D ADJUSTMENTS MADE IN ANALYSIS

1 What factors were adjustments made for?

2 How was this data obtained?

3 What statistical methods were used for the adjustments?

4 What grade does this correspond with?

E RESULTS

1 How many patients in the high volume group?

2 How many patients in the low volume group?

3 What is the crude mortality rate in the high volume group? How many deaths is this?

4 What is the crude mortality rate in the low volume group? How many deaths is this?

5 What is the adjusted mortality rate in the low volume group? Approximately how many deaths is this?

6 What is the crude odds ratio for volume?

7 What is the adjusted odds ratio for volume?

F OTHER INFORMATION

1 Does the paper report on physican volume? Whatevidence does it report?

2 Other comments

(NHS Centre for Reviews and Dissemination 1996)

Appendix 3

Details of calculations for economic analyses

Costs of monitoring

Test CSA	Unit cost	First visit	Repeat visit
Urea/elecs/creat	2.96	2.96	2.96
Pregnancy	6.17	3.09	0
GFR	8	8	0
		14.05	2.96
MTX			
FBC	1.89	1.89	1.89
Biochem profile	8.08	8.08	8.08
PIIINP	8	8	8
Pregnancy	6.17	3.09	0
Liver biopsy	**600**		
		21.06	17.97
Acitretin			
FBC	1.89	1.89	1.89
Biochem profile	8.08	8.08	8.08
Lipid profile	5.85	5.85	5.85
X-ray spine	**106**	**106**	0
Pregnancy	6.17	3.09	0
		124.91	15.82
PUVA			
Biochem profile	8.08	8.08	0

Note: All routine biochemistry, haematology, radiology etc costs are accounted for in the fully-absorbed clinic visit cost of £76.00. Therefore, only exceptional or unusual items (shown in bold) have been added in the analyses.

Drug costs						
Drug	Strength	Pack size	Price	Unit price	Dose	Cost/12wks treatment
MTX	2.5	100	11.41	0.1141	15mg/wk	8.22
MTX	10	100	55.07	0.5507	20mg/wk	13.22
Neoral	100	30	76.33	2.544333	400mg/d	854.90
Neoral	100	30	76.33	2.544333	300mg/g	641.17
Neoral	50	30	40.22	1.340667		
Acitretin	10	56	25.34	0.4525		
Acitretin	25	56	58.8	1.05	75mg/d	264.60
Acitretin	25	56	58.8	1.05	50mg/d	176.40
Folic acid	5	20	0.49	0.0245		2.06

Cyclosporin primary - methotrexate secondary treatment	
Pathway	**Cost elements**
1	12 visits + 12 wks CSA
2	12 visits + 2 x 12 wks CSA
3	12 visits + 2 x 12 wks CSA + 12wks MTX
4	12 visits + 2 x 12 wks CSA + 12wks MTX
5	12 visits + 12 wks CSA + 12wks MTX
6	12 visits + 12 wks CSA + 2 x 12wks MTX
7	12 visits + 12 wks CSA + 2 x 12wks MTX
8	12 visits + 12 wks CSA + 12 wks MTX

Note: All methotrexate treatment costs included the cost of concomitant folic acid treatment (5mg daily).

Methotrexate primary - cyclosporin secondary treatment	
Patway	**Cost elements**
1	12 visits + 2 x 12 wks MTX (15mg/wk) + 2 x 12 wks MTX (15mg/wk)
2	12 visits + 2 x 12 wks MTX (15mg/wk) + 1x 12 wks MTX (20mg/wk) + 1 x12 wks MTX 15mg/wk
3	12 visits + 2 x 12 wks MTX (15mg/wk) + 1x 12 wks MTX (20mg/wk) + 1 x12 wks CSA
4	12 visits + 2 x 12 wks MTX (15mg/wk) + 1x 12 wks MTX (20mg/wk) + 1 x12 wks CSA
5	12 visits + 1 x 12 wks MTX (15mg/wk) + 1 x 12 wks CSA
6	12 visits + 1 x 12 wks MTX (15mg/wk) + 2 x 12 wks CSA
7	12 visits + 1 x 12 wks MTX (15mg/wk) + 2 x 12 wks CSA
8	12 visits + 1 x 12 wks MTX (15mg/wk) + 1 x 12 wks CSA

Acitretin primary - cyclosporin secondary treatment	
Pathway	**Cost elements**
1	12 visits + 2 x12 wks ACI (50mg/d) + spine Xray + 2 x 12 wks ACI (50mg/d)
2	12 visits + 2 x12 wks ACI (50mg/d) + spine Xray + 1 x 12 wks ACI 75mg/d + 1 x 12 wks ACI (50mg/d)
3	12 visits + 2 x12 wks ACI (50mg/d) + spine Xray + 1 x 12 wks ACI 75mg/d + 1 x 12 wks CSA
4	12 visits + 2 x12 wks ACI (50mg/d) + spine Xray + 1 x 12 wks ACI 75mg/d + 1 x 12 wks CSA
5	12 visits + 1 x12 wks ACI (50mg/d) + spine Xray + 1 x 12 wks CSA
6	12 visits + 1 x12 wks ACI (50mg/d) + spine Xray + 2 x 12 wks CSA
7	12 visits + 1 x12 wks ACI (50mg/d) + spine Xray + 2 x 12 wks CSA
8	12 visits + 1 x12 wks ACI (50mg/d) + spine Xray + 1 x 12 wks CSA

PUVA primary - cyclosporin secondary treatment	
Pathway	**Cost elements**
1	12 visits + 20 PUVA sessions
2	12 visits + 2 x 20 PUVA sessions
3	12 visits + 2 x 20 PUVA sessions + 1 x 12wks CSA
4	12 visits + 2 x 20 PUVA sessions + 1 x 12wks CSA
5	12 visits + 20 PUVA sessions + 1 x 12wks CSA
6	12 visits + 20 PUVA sessions + 2 x 12 wks CSA
7	12 visits + 20 PUVA sessions + 2 x 12 wks CSA
8	12 visits + 20 PUVA sessions + 1 x 12 wks CSA

Calculation of the cost-effectiveness ratio:

1. For each pathway the cumulative probability of the outcome is calculated by multiplying the probabilities for each stage.
2. The probabilities for all the successful outcomes are then added together to give the overall probability of success. The process is repeated for the pathways that end in failure. (See Chapter 1, Table 1.1). The sum of the overall probabilities of success and failure must be equal to one.
3. The cost of each pathway is calculated by multiplying the cumulative probability for the pathway by the sum of all the cost elements in the pathway.
4. The total cost of treatment is the sum of the costs of each pathway.
5. The cost effectiveness ratio is calculated by dividing the total cost by the cumulative success rate, which gives a "cost per success".