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**APPLYING QUANTITATIVE METHODS IN THE
ASSESSMENT OF OUTCOMES OF
PHARMACOTHERAPY OF PSORIASIS**

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November 1999

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The University of Aston in Birmingham
Applying quantitative methods in the assessment of outcomes of
pharmacotherapy of psoriasis

Darren Mark Ashcroft
Doctor of Philosophy 1999

Healthcare providers and policy makers are faced with an ever-increasing number of medical publications. Searching for relevant information and keeping up to date with new research findings remains a constant challenge. It has been widely acknowledged that narrative reviews of the literature are susceptible to several types of bias and a systematic approach may protect against these biases. The aim of this thesis was to apply quantitative methods in the assessment of outcomes of topical therapies for psoriasis. In particular, to systematically examine the comparative efficacy, tolerability and cost-effectiveness of topical calcipotriol in the treatment of mild-to-moderate psoriasis.

Over the years, a wide range of techniques have been used to evaluate the severity of psoriasis and the outcomes from treatment. This lack of standardisation complicates the direct comparison of results and ultimately the pooling of outcomes from different clinical trials. There is a clear requirement for more comprehensive tools for measuring drug efficacy and disease severity in psoriasis. Ideally, the outcome measures need to be simple, relevant, practical, and widely applicable, and the instruments should be reliable, valid and responsive.

The results of the meta-analysis reported herein show that calcipotriol is an effective antipsoriatic agent. In the short-term, the pooled data found calcipotriol to be more effective than calcitriol, tacalcitol, coal tar and short-contact dithranol. Only potent corticosteroids appeared to have comparable efficacy, with less short-term side-effects. Potent corticosteroids also added to the antipsoriatic effect of calcipotriol, and appeared to suppress the occurrence of calcipotriol-induced irritation. There was insufficient evidence to support any large effects in favour of improvements in efficacy when calcipotriol is used in combination with systemic therapies in patients with severe psoriasis. However, there was a total absence of long-term morbidity data on the effectiveness of any of the interventions studied.

Decision analysis showed that, from the perspective of the NHS as payer, the relatively small differences in efficacy between calcipotriol and short-contact dithranol lead to large differences in the direct cost of treating patients with mild-to-moderate plaque psoriasis. Further research is needed to examine the clinical and economic issues affecting patients under treatment for psoriasis in the UK. In particular, the maintenance value and cost/benefit ratio for the various treatment strategies, and the assessment of patient's preferences has not yet been adequately addressed for this chronic recurring disease.

Key words : *psoriasis, meta-analysis, outcome measure, quality of life, cost-effectiveness*

To Linda, Olivia, and my parents

ACKNOWLEDGEMENTS

I would like to thank Professor Alain Li Wan Po, my supervisor, for his kind assistance and guidance throughout the course of my PhD studentship.

Grateful thanks are also extended to Professor Hywel Williams and Professor Christopher Griffiths for their pertinent comments, help and encouragement.

The studentship from Boots Healthcare International is also gratefully acknowledged.

ABBREVIATIONS

APC	antigen presenting cell
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CIA	computer image analysis
CPT	calcipotriol
CSM	Committee on Safety of Medicines
d	mean difference in effect
DB-B	double blind bilateral
DB-P	double blind parallel
DIDS	Dermatology Index of Disease Severity
DLQI	Dermatology Life Quality Index
DQOLS	Dermatology Quality of Life Scales
GHQ	General Health Questionnaire
HLA	human lymphocyte antigen
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
IL	interleukin
lnRR	log to base e of the rate ratio
MOP	methoxypsoralen
MPD	minimal phototoxic dose
MTX	methotrexate
NHP	Nottingham Health Profile
NNT	number needed to treat
Open-B	open bilateral
PASI	Psoriasis Area and Severity Index
PDI	Psoriasis Disability Index
PGI	Patient Generated Index
PIIINP	aminoterminal peptide of type III procollagen
PLSI	Psoriasis Life Stress Inventory

PUVA	psoralen and ultraviolet A
QALY	quality adjusted life year
QoL	quality of life
r	Pearson correlation coefficient
r_s	rank-order correlation coefficient
RCTs	randomised controlled trials
RD	rate difference
RR	rate ratio
SAPASI	Self-administered Psoriasis Area and Severity Index
SB	single blind
SD	standard deviation
SE	standard error
SF-36	Short Form-36 Health Survey
TIG	tazarotene-induced gene
UKSIP	United Kingdom Sickness Impact Profile
UVA	ultraviolet A
UVB	ultraviolet B
WHO	World Health Organisation
z	standard normal statistic
95% CI	95% confidence interval
χ^2	chi-squared statistic
ω_i	weight : inverse of the squared SE of the difference in response

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CHAPTER 1

Psoriasis - The disease and its treatment

1.1 Introduction

Psoriasis is a common skin disorder characterised clinically by indurated, erythematous scaling plaques most commonly located on the extensor aspects of the elbows and knees, and scalp, but any skin site may be affected. In the United Kingdom, the prevalence of psoriasis in the general population varies from 1.48 to 1.6% in published reports, with men and women affected in equal numbers (Nevitt & Hutchinson 1996, Rea *et al.* 1976). In the United States, the Health and Nutrition Examination Survey (HANES I) examined 20,749 individuals, finding a prevalence of 1.43% (Johnson 1978). Psoriasis causes substantial morbidity and many patients experience psychological stress. The condition is chronic for the majority of sufferers, but periods of remission and relapse profile the course of the disease. It also has considerable economic consequences, including loss of earnings, cost of care, and cost of drug treatment.

There are several clinical presentations, including guttate, pustular and erythrodermic variants. Inflammatory changes can affect the joints producing psoriatic arthritis in approximately 6% of sufferers (Camisa 1994). Patients

may also progress from one clinical presentation to another during their lifetime. In this thesis, the focus is principally on the most common presentation, chronic plaque psoriasis.

1.2 Aetiology and pathogenesis

Census, twin and human lymphocyte antigen (HLA) studies have clearly indicated a genetic component in the pathogenesis of psoriasis. A recent Swedish study among first-degree relatives of 3095 sufferers found that the lifetime risk of a child developing psoriasis if neither of the parents has the disease is 0.04; if one parent has it the risk rises to 0.28; if both have it the risk is 0.65 (Swanbeck 1997). There is also a 72 per cent concordance of occurrence between pairs of monozygotic twins (Farber & Nall 1971). This concordance rate implies that environmental factors are important for disease expression in genetically predisposed individuals. The relative risk of acquiring psoriasis is increased by the presence of specific HLA markers particularly Cw6, which is present in 85% of patients with early onset psoriasis (Tiilikainen *et al.* 1980). Three chromosomal loci have been genetically linked to psoriasis, namely 6q, 17q and 4q, designated psoriasis genes 1,2 and 3, respectively. Several other genetic linkages are proposed on chromosomes 1,2,6,8,16 and 20. Environmental factors such as physical trauma (Koebner phenomenon), infection (β -haemolytic streptococci, HIV), drugs (lithium, β -blockers, chloroquine, mepacrine) and psychological stress

have also been linked with initiating the disease.

Patients with chronic plaque psoriasis have been divided into two groups based on peak occurrences in adolescents and young adults (16-22 years of age) and older individuals (57-60 years) (Henseler & Christophers 1985). With earlier onset, there is a strong family history of psoriasis, a high incidence of HLA-Cw6 and the disease is generally more aggressive. In contrast, with late onset, there is little or no family history, a normal incidence of HLA-Cw6 and more stable disease. The extent to which genetic and environmental factors interact to cause these differences has not been determined.

The histological hallmarks of psoriasis include abnormal keratinocyte differentiation and hyperproliferation, infiltration of inflammatory cells and vascular proliferation. The cell cycle of keratinocytes is reduced from 311 to 36 hours and the time for epidermal keratinocyte transit decreased from 27 days to 4 days (Ortonne 1996). Epidermal keratinocyte proliferation results from the release of cytokines produced by leucocyte activated T-cells. The cytokine profile within a psoriatic plaque is of a Th1 profile, ie. γ -interferon, IL-2. IL-8 is also a key cytokine to the process as it acts both as a T-cell chemoattractant and stimulates keratinocyte proliferation. As yet, the pathogenesis is not fully understood and, in particular, it has not been established whether the primary abnormality involves keratinocytes, dermal fibroblasts, immune cells or a combination of these factors.

1.3 Present treatment options

The treatments currently available for psoriasis are only suppressive, not curative. When provided with this information and cautioned on the potential adverse effects of certain drugs, many patients with limited disease will often choose to live with their condition (Greaves & Weinstein 1995). Specific intervention with antipsoriatic therapies should be tried for those patients whose local symptoms (such as itching, pain, prominent lesions) or psychological status (embarrassment over appearance, fear of rejection) proves problematic. Figure 1.1 illustrates the current therapeutic options in psoriasis.

In selecting a suitable agent, consideration should be given to the overall extent of the disease, the body areas involved, the patient's age, sex, general health, knowledge, previous treatment and preferences. Topical treatments are first-line therapy for patients with mild to moderate plaque psoriasis. In cases of severe, extensive psoriasis where topical therapy is either impractical or not sufficiently effective, systemic treatment may be warranted at the outset.

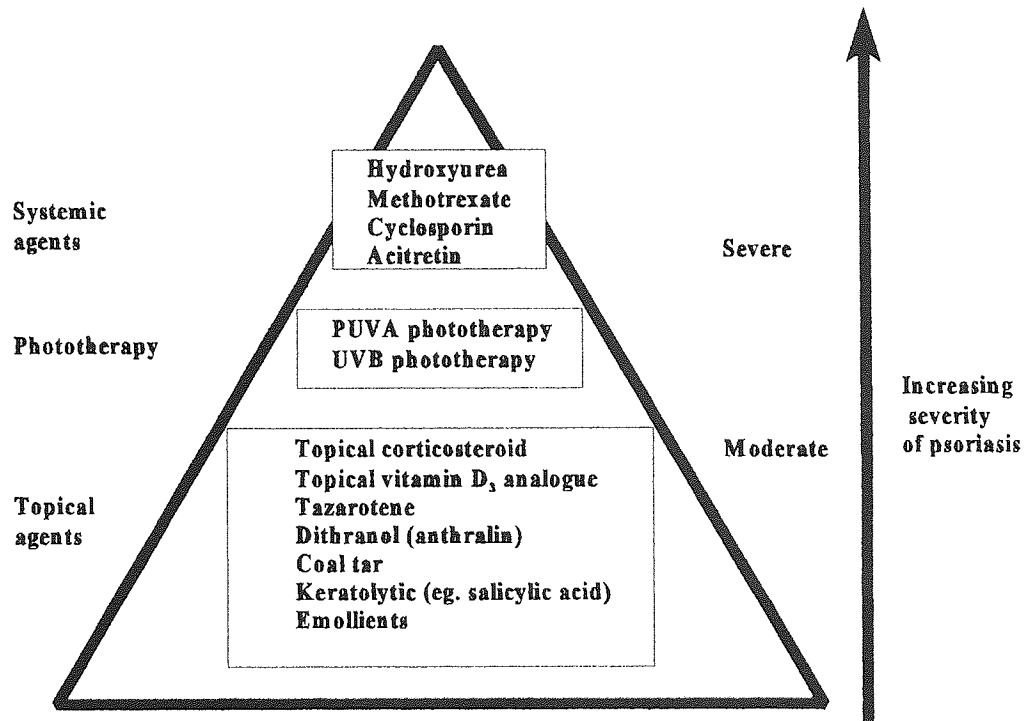


Figure 1.1 : Current treatment options for psoriasis.

1.3.1 Topical treatment

The topical agents available for the treatment of psoriasis include emollients, keratolytics, coal tar, topical corticosteroids, dithranol, topical vitamin D₃ analogues and tazarotene. Strategies for maximising the response to topical therapy include :

- Clear guidance on use
- Check compliance
- Supervised treatment
- Inpatient treatment
- Combined topical modalities
- Occlusion
- High dose therapy

Emollients

In mild psoriasis, an emollient may be the only treatment required. These agents hydrate the stratum corneum and facilitate desquamation. Most emollient agents are mineral oils and paraffins in an oil-in-water emulsion. Preparations such as aqueous cream can be used as soap substitutes and other general measures include the use of moisturising bath additives. As yet, there is a lack of published comparative trials which examine the efficacy of different emollients in psoriasis. However, the addition of a water-in-oil

emollient to a once daily application of betamethasone dipropionate cream can reduce the degree of dryness, scaling and induration (Watsky *et al.* 1992). This effect may result from inhibition of arachidonic acid oxidation thereby blocking the production of inflammatory cytokines (Penneys *et al.* 1980). Occasionally, some ingredients can cause sensitisation, for instance hydrous wool fat (lanolin).

Salicylic acid

Salicylic acid, in concentrations of 2 to 6%, is often applied to areas of thick scale, such as the palms, soles and scalp, either alone or in combination with coal tar, topical corticosteroids or dithranol. It acts as a keratolytic and enhances the efficacy of these agents by increasing their skin penetration, but there are no randomised controlled trials to show that it is effective as a single agent in patients with psoriasis (Greaves & Weinstein 1995). When used in higher concentrations, salicylic acid is irritant and there is a potential risk of salicylate toxicity when applied extensively.

Coal tar

Coal tar preparations are generally applied to the body once or twice daily. Treatment usually starts with concentrations of 0.5 to 1.0% crude coal tar with incremental increases in strength according to tolerance and efficacy every few days. Coal tar preparations of between 1 and 5% are as effective as higher concentrations up to 25% (Gawkrodger *et al.* 1997). When lesions are widespread, coal tar baths are useful. The preparations are often messy, stain

clothing and are limited by their unpleasant odour. Newer formulations based on refined coal tars, such as coal tar solution, are generally more aesthetically acceptable to patients, but are also less efficacious (Kanzler & Gorsulowsky 1993).

Coal tar can cause irritation and should therefore be used with caution on the face and flexures and avoided in unstable psoriasis. Other potential effects include acneform eruptions, folliculitis and photosensitivity. The use of coal tar shampoos can result in the percutaneous absorption of polycyclic aromatic hydrocarbons which are known to be carcinogenic (van Schooten 1995). However, no epidemiological evidence has clearly shown that topical coal tar alone increases the risk of carcinoma (Gawkrodger *et al.* 1997).

Dithranol (anthralin)

Traditionally, dithranol has been used according to the Ingram regimen - daily coal tar baths and UVB phototherapy followed by the 24-hour application of dithranol paste - as the standard inpatient treatment for widespread disease. Treatment generally commences with a concentration of 0.1% and the strength of the preparation is progressively increased (eg. every 5 days) depending upon the degree of irritation and the clinical response. In the short-contact regimen, dithranol is applied for a 15-60 minute period, allowing drug penetration of lesional but not perilesional skin, without a reduction in efficacy (Ryatt *et al.* 1984). Moreover, the shorter application times have proved more convenient and acceptable to patients.

Dithranol is oxidised to form highly reactive free radical compounds that are thought to inhibit DNA synthesis. It stains the skin and clothing, and can irritate perilesional skin causing inflammation. It should therefore not be applied to the face, flexures or unstable psoriasis. The use of wash-off solutions containing triethenolamine can reduce the degree of irritation (Gawkrodger *et al.* 1997).

Topical corticosteroids

Topical corticosteroids are the most widely prescribed treatment for psoriasis in the USA (1992 data) (Liem *et al.* 1992). In the UK, dermatologists tend to reserve their use for resistant conditions and sites where other topical agents are poorly tolerated such as the face, scalp and flexures. A wide range of preparations are available which differ in efficacy. Topical corticosteroids cause vasoconstriction which correlates well with clinical efficacy and has been used to rank the potency of different preparations. There is some evidence that once daily application of topical corticosteroids is as effective as twice daily treatment and may have fewer adverse effects (Lagos & Maibach 1998). In addition, the cost of treatment will be reduced and patient compliance may improve.

Corticosteroids have anti-inflammatory, anti-proliferative and immunosuppressive activities which are likely to be important in explaining their antipsoriatic action. Local side-effects include dermal atrophy, striae, telangiectasia, acneform eruptions, perioral dermatitis, hypopigmentation,

tachyphylaxis and masking of local infections (Katz 1995). These risks are related to the potency, the quantity applied and the concomitant use of occlusion. On rare occasions, systemic absorption of topical corticosteroids has been reported to precipitate adrenal suppression (Gawkrodger *et al.* 1997, Katz 1995).

Vitamin D₃ analogues

The topical vitamin D₃ analogues include calcipotriol and tacalcitol, which act predominantly by inhibiting epidermal cell proliferation and enhancing cell differentiation. Interest first arose in the use of vitamin D₃ when a patient's psoriasis improved while being treated with 1 α -hydroxy-vitamin D₃ for osteoporosis (Morimoto & Kumahara 1985). This serendipitous observation led to the search for a vitamin D₃ analogue which had minimal effects on calcium metabolism. Nowadays, the topical vitamin D₃ analogues are regarded by many to be the first-line treatment for mild-to-moderate plaque psoriasis. There is little published experience of the use of the topical vitamin D₃ analogues in types of psoriasis other than chronic plaque psoriasis.

Calcipotriol is licensed for once or twice daily use in mild-to-moderate plaque psoriasis affecting up to 40% of the skin surface. It is available in a scalp solution, ointment and cream, but it is recommended that the maximum weekly dose should not exceed 100g ointment or cream. However, there are published reports on the use of high dose therapy in the inpatient management of severe psoriasis (Bourke *et al.* 1993). Tacalcitol is licensed in the UK for

once daily treatment, preferably at bedtime. It is recommended that the rate of application of tacalcitol should not exceed 5g of ointment per day. One of the main advantages of the vitamin D₃ analogues is that they are more aesthetically acceptable to patients than some of the older topical treatments, notably crude coal tar and dithranol. However, lesional and perilesional irritation are reported to be the most common side-effects in clinical trials. This precludes the use of calcipotriol on facial lesions and the flexures.

Tazarotene

Tazarotene is the first topical retinoid to be licensed for the treatment of mild-to-moderate plaque psoriasis affecting up to 10% of the skin surface. It normalises keratinocyte differentiation and proliferation by inducing expression of three tazarotene-induced genes (TIG) in the epidermis (Duvic *et al.* 1997). It is recommended that tazarotene gels (0.05% or 0.1%) are applied to psoriatic lesions once daily for a period of up to 12 weeks. By far, the most common adverse effects include pruritus, burning, erythema, and irritation. These effects are mainly of mild-to-moderate severity and dose-dependent. Indeed, tazarotene should not be applied to the face, intertriginous areas, or scalp. Pregnancy and lactation are also specific contraindications to use since there is clear evidence that retinoids are teratogenic.

1.3.2 Phototherapy and systemic treatments

Treatment options include UVB phototherapy, photochemotherapy (PUVA), methotrexate, cyclosporin, acitretin, and hydroxyurea. The choice must be tailored for each patient since all systemic agents can be accompanied by potentially serious side-effects and specific contraindications (Table 1.1).

Strategies for dose-sparing include :

- Maximise efficacy of topical therapy
- Use lowest effective dose at all times
- Intermittent therapy
- Combination therapy
- Rotational therapy

Table 1.1 : Systemic treatments used for psoriasis

Treatment	Dosage	Contraindications	Precautions and monitoring
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Adapted from Gawkrödger *et al.* 1997

Phototherapy

Ultraviolet B radiation is especially useful in the management of moderate to severe, guttate and chronic plaque psoriasis. It is indicated in patients whose disease is refractory to topical therapy or widespread psoriasis in which application of topical medications would be impractical (eg. guttate psoriasis), leading to problems with compliance. Treatment is usually given two or three times each week in doses sufficient to produce minimal erythema. In the Goeckerman regimen, coal tar is applied before daily exposure to UVB radiation. Remission can be achieved in at least 80% of patients when coal tar is used in conjunction with phototherapy (Stern *et al.* 1986). However, efficacy can be reduced by a number of commonly used emollients, such as white and yellow soft paraffin, which block the penetration of ultraviolet light. Coconut oil has been recommended as a suitable pre-treatment emollient (Williams 1991).

Narrowband UVB phototherapy at the 311nm region has been reported to produce a greater improvement in psoriasis when compared to traditional broadband UVB sources (290-320 nm) (British Photodermatology Group 1997). As yet, the comparative efficacy has not been confirmed in head-to-head randomised controlled trials. Phototherapy must be carefully regulated, owing to the short-term risks of erythema and vesiculation and the long-term risks which include premature skin ageing. Furthermore, UVB is contraindicated in patients with photosensitivity disorders, such as lupus erythematosus.

Photochemotherapy

Photochemotherapy combines long wave (320-400nm) ultraviolet A irradiation with the oral or topical administration of psoralens (PUVA). The two agents used, 5- and 8-methoxypsoralen (MOP) are not licensed in the UK. MOP is believed to intercalate into DNA, forming cross-links between DNA strands. Activation of MOP by UVA radiation, disrupts DNA synthesis thereby inhibiting cell proliferation. The initial UVA exposure should be determined by prior measurement of the minimal phototoxic dose (MPD), rather than on skin type (British Photodermatology Group 1994). UVA dose increments are then calculated as a percentage of the previous dose. Twice weekly PUVA has been recommended as the optimal treatment regimen; lower cumulative UVA doses are required for clearance and more efficient use of PUVA services are possible when compared to treatment given three times weekly (British Photodermatology Group 1994).

Commonly, PUVA causes nausea, pruritus and erythema. Other short-term risks include acneform eruptions, the Koebner reaction, headache and skin pain (Wolff 1990). The long-term risks include the development of actinic keratoses, widespread PUVA lentiginos, premature ageing of the skin and irregular pigmentation. Cataracts may occur in patients who fail to wear suitable UVA eye protection for 12 to 24 hours following oral psoralen ingestion. PUVA therapy increases the risk of non-melanomatous skin cancer, particularly squamous cell carcinoma (Stern & Laird 1994). There is also an increased risk of malignant melanoma (Stern *et al.* 1997). In men, there is a

higher incidence of genital skin cancer; it is therefore advised that genitalia be shielded during treatment (British Photodermatology Group 1994).

Maintenance PUVA should be avoided, whenever possible, to minimise the cumulative lifetime dose of UVA irradiation. Patients who have received more than 150 treatments should have an annual examination for premalignant or malignant skin lesions (British Photodermatology Group 1994).

Methotrexate

Methotrexate (MTX) is indicated for the treatment of recalcitrant psoriasis, unresponsive to topical therapy. It is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase, thereby blocking an essential step in DNA synthesis. It is probable that MTX works in psoriasis by virtue of its immunomodulatory properties. MTX is considered by many the “gold standard” on the basis of its therapeutic effectiveness in severe psoriasis, but there are no controlled trials that examine its efficacy against other systemic treatments in chronic plaque psoriasis. MTX is administered as a once weekly oral dose, usually 5-20mg. Prior to starting treatment, a test dose 2.5-5mg, is given to detect idiosyncratic responses. If tolerated MTX is probably the preferred treatment for long-term use.

Long-term treatment is accompanied with a risk of hepatotoxicity. Because of this, patients are advised to avoid alcohol intake whilst taking MTX. The American Academy of Dermatology (1988) recommend a liver biopsy at or

near the beginning of treatment and after each cumulative dose of 1.0 to 1.5g of MTX (Roenigk *et al.* 1988). However, recent studies have proposed that routine liver biopsy need no longer be performed in closely monitored patients receiving low-dose MTX since the risks of development or progression of hepatic disease are small in relation to the cost and morbidity of the procedure (Boffa & Chalmers 1996). Although not widely implemented, there is evidence that an amino propeptide of type III procollagen (PIIINP) assay can be performed 3-monthly and liver biopsy considered only for those patients with persistently abnormal results (Gawkrödger *et al.* 1997). Other important side effects include nausea, leucopenia and thrombocytopenia. Daily folic acid, 5mg, may significantly reduce side-effects, especially nausea. The Committee on Safety of Medicines (CSM) have identified 83 cases of blood dyscrasias amongst patients receiving low-dose MTX, of which 36 had a fatal outcome (CSM 1994). MTX has not been proved to be carcinogenic at the dosages used in psoriasis but it is teratogenic (Boffa & Chalmers 1996). It should therefore not be used in pregnant or breast-feeding patients and conception should be avoided for at least three months after cessation of treatment in either sex.

There are a number of important potential drug interactions with MTX that may result in drug toxicity. In particular, drug interactions can occur with the concomitant administration of salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), penicillins, trimethoprim, co-trimoxazole, probenecid, acitretin and cyclosporin. Interaction is due to drug displacement and/or

competition for renal tubular secretion. Retinoids increase plasma MTX concentrations and the risk of hepatotoxicity. MTX and cyclosporin may inhibit each other's elimination and produce additive immunosuppression.

Cyclosporin

Cyclosporin is licensed for the treatment of severe psoriasis in patients whom conventional therapy is either ineffective or inappropriate. By blocking cytoplasmic calcineurin phosphatase, cyclosporin inhibits the production of interleukin-2 (IL-2) and thereby T-cell activation. Indeed, it was by demonstrating the efficacy of cyclosporin in the treatment of psoriasis that the T-cell hypothesis of psoriasis pathogenesis was proved. Cyclosporin is taken at a low (2.5-5mg/kg/day) dose. As a result of concerns about toxicity associated with long-term treatment, most dermatologists nowadays recommend short-term intermittent treatment, ie. 3-4 months treatment at a time. Regular monitoring of the patient during treatment with cyclosporin is essential, since dose-dependent renal impairment is the most common cause of withdrawal of treatment. Renal biopsy findings have confirmed nephropathy in patients on long-term cyclosporin for psoriasis (Zachariae *et al.* 1997). Hypertension (sustained diastolic blood pressure over 95 mmHg) is also dose-dependent and can be treated by dose reduction or concomitant antihypertensive therapy. Other side effects include hepatotoxicity, hypertrichosis, gingival hyperplasia, gastrointestinal disturbances (nausea, abdominal pain, diarrhoea) and central nervous system disorders, including tremor and paraesthesia (Gawkrodger *et al.* 1997). In transplant patients, the

use of cyclosporin is associated with an increased incidence of malignancy, notably lymphoma and cutaneous tumours. Whether this risk is increased in psoriatic patients receiving low dose cyclosporin remains to be determined.

Many drugs affect cyclosporin blood concentrations by competitive inhibition or induction of cytochrome P450 liver enzymes. Increased plasma concentrations have been reported following the concurrent administration of calcium-channel antagonists (diltiazem, nifedipine, verapamil), doxycycline, erythromycin, oral contraceptives and ketoconazole. Enzyme-inducing drugs which include carbamazepine, rifampicin, phenytoin and phenobarbitone may lower cyclosporin blood levels. In addition, several drugs (aminoglycosides, amphotericin, ciprofloxacin, trimethoprim, NSAIDs) may enhance cyclosporin-induced nephrotoxicity. Grapefruit juice has also been reported to increase plasma cyclosporin concentrations.

Acitretin

Acitretin is a synthetic retinoid which is used for the treatment of severe, recalcitrant psoriasis. In the UK, its availability is restricted to hospitals or specified community pharmacies at the request of a consultant dermatologist. The efficacy of acitretin alone is limited, but tends to be most effective in cases of erythrodermic or pustular psoriasis. Unlike cyclosporin and MTX it is slower in onset of action. Combination therapy with acitretin and PUVA can enhance the therapeutic effects whilst minimising the dosage of each treatment. Such combinations have proved especially useful in the treatment

of recalcitrant plaque psoriasis and palmoplantar pustulosis. Similar results have also been reported for acitretin combined with UVB phototherapy (Iest & Boer 1989).

Women of child-bearing potential must use effective contraception for at least two years after withdrawal of therapy as acitretin is teratogenic (Gawkrodger *et al.* 1997). Dryness of the mucous membranes of the eyes, nose and lips occurs almost universally. Other common adverse effects include elevation of liver enzymes, skin peeling, and alopecia (Halioua & Saurat 1990).

Hyperlipidaemia may occur, particularly in patients with a history of lipid disorders, high alcohol intake, diabetes mellitus, obesity and smoking.

Skeletal alterations associated with long-term use include ligamentous calcification and hyperostoses (Gollnick 1996).

Hydroxyurea

Hydroxyurea is not licensed for the treatment of psoriasis in the UK. It is generally considered to be a third-line agent, used only in situations where other systemic agents have failed or are contraindicated. The main concern is the risk of myelosuppression which can manifest as megaloblastic anaemia, thrombocytopenia or leucopenia.(Gawkrodger *et al.* 1997). Other reported side effects have included diffuse hyperpigmentation, fever, alopecia, elevation of liver enzymes and nausea (Boyd & Neldner 1991). Patients need to be closely monitored and the drug is best avoided in women of childbearing age due to the potential risks of teratogenicity.

Systemic corticosteroids

The use of oral corticosteroids in the treatment of psoriasis is limited and potentially dangerous. Their adverse effects are well documented, but there is a serious risk of rebound flaring of psoriasis on discontinuation which may lead to severe, recalcitrant, generalised, pustular forms of the disease. It is therefore recommended that systemic corticosteroid therapy should only be initiated in the following circumstances (Gawkrodger *et al.* 1997) :

- 1 Persistent, otherwise uncontrollable, erythrodermic psoriasis causing metabolic complications.
- 2 Generalised pustular psoriasis, when other drugs are contraindicated or ineffective.
- 3 Severe psoriatic polyarthritis threatening severe irreversible joint damage.

1.4 Future treatment prospects

Psoriasis is unlikely to be caused by genetic influence alone, so identifying possible environmental trigger factors will be important, and their removal or modification will be an essential part of future treatment. In particular, studies have suggested that patients under stress can respond poorly to treatment. Further research is warranted to examine whether stress management techniques can facilitate psychological adaptation and thereby improve the

therapeutic outcome from treatment.

Based on our current knowledge of pathogenesis in psoriasis, drugs that prevent or reduce T-cell activation or which block T-cell binding to antigen-presenting cells (APC) should be of value. Cyclosporin and tacrolimus have already been shown to improve severe psoriasis in a substantial proportion of patients when used alone. The usefulness of these agents, however, is often restricted by their toxicity. Developing agents which specifically target the T-cell may minimise many of the untoward effects of treatment. In particular, an agent known as LFA3-TIP has proved promising in early clinical studies when administered as a weekly intravenous dose.

In patients with atopic dermatitis, high levels of Th2 cytokines are present and there is some evidence that administration of gamma interferon, a Th1 cytokine, is an effective treatment. Interestingly, there appears to be a reciprocal relationship in psoriasis in which Th1 cytokine levels are elevated. This raises the prospect that administration of a Th2 cytokine, for example interleukin 10 (IL10), might prove effective in the treatment of psoriasis. Finally, it has been suggested that giving an antigen orally in low-dose may induce an immune response that triggers the release of high levels of Th2 cytokines. The development of such treatments is obviously limited by our knowledge of the aetiology and pathogenesis of psoriasis. At present, no specific antigen has been identified, but it has been proposed that a component of keratin might be a suitable candidate.

CHAPTER 2

Clinical measures of disease severity and outcome in psoriasis : a critical appraisal of their quality

2.1 Introduction

Outcomes in clinical trials of patients with psoriasis have been measured using a wide range of techniques, but there has been a lack of standardisation which complicates the direct comparison of results and ultimately the pooling of outcomes from different clinical trials (Marks *et al.* 1989). Many of the techniques were developed for use in specific trials but provided limited or no data on their validity and reliability. Thus, many of the existing outcome measures cannot be assumed to be reliable and valid measures of clinical severity.

Generally, simple objective parameters, such as the number of patients who are cleared of the disease or the number of patients who have relapsed, which are easily understood should be chosen (Bigby & Gadenne 1996). However, psoriasis is a chronic condition characterised by fluctuations in clinical severity for which current treatments are usually only capable of producing incremental improvements. Many of the techniques used for assessing the effect of treatment rely on subjective assessments of clinical response by

doctors and patients. Although methods have been recommended to evaluate the psychometric properties of scales (Hays *et al.* 1993), there are still substantial shortcomings in their application. This chapter reports on the range of clinical outcome measures used in psoriasis research and provides a critical appraisal of their quality.

2.2 The quality of an outcome measure : reliability and validity

Reliability is the extent to which a measuring procedure yields the same results on repeated use under the same conditions. The dimensions include test-retest reliability, internal consistency and interobserver reliability.

Validity refers to the ability of an instrument to measure what it is designed to measure. This distinction is important since an outcome measure may be reliable (i.e. produce the same score under identical conditions), but it may be consistently measuring the wrong construct (i.e. not what it is designed to measure) (Hays *et al.* 1993). Ease of use and clinical relevance are also important additional considerations. Table 2.1 lists the principal criteria for evaluation of measures.

Table 2.1 : Principal requirements of outcome measures

Properties	Characteristics
<i>Reliability:</i>	
Internal consistency	Indicator of how well the items in an instrument intercorrelate, thereby measuring the same construct, i.e psoriasis disease severity.
Test-retest	Measurement of the stability of the severity scores over time.
Interobserver	Level of agreement between multiple observers on the assignment of severity ratings.
<i>Validity:</i>	
Content	Examination of whether items in an instrument adequately represent the underlying construct.
Criterion	Correlation between a “gold standard” measure and the instruments rating.
Construct	Correlation between the instrument and other variables, consistent with theoretically-derived predictions.
<i>Sensitivity to change</i>	The ability of an instrument to detect clinically meaningful changes in severity.

Typically, Pearson (r) or rank-order (r_s) correlation coefficients have been used to report on reliability and validity results, but they should be interpreted cautiously. Pearson correlations quantify the *association* between two measurement scales, but do not indicate *agreement*. A perfect correlation requires only that the pairs of readings lie along a straight line, not necessarily the line of equality. In contrast, the intraclass correlation coefficient (ICC) measures the average similarity of the actual scores on the two ratings, not merely the similarity of their relative standings (McDowell & Newell 1996). Alternative approaches for assessing agreement between two methods of clinical measurement have also been proposed by Bland & Altman (1986). They recommend a plot of the difference between the measures against their mean value.

2.3 Clinical Evaluations

Traditionally, assessments of psoriatic severity have relied on the ability of the clinician to rate the visible signs of the disease (eg. involved body surface area, erythema, plaque thickness, scaling) to produce a severity score. Global assessments have also been extensively used. Typically, this involves grading at specified time points to assess the level of improvement or deterioration from the baseline condition. Both clinician and patient-rated scales have been developed, but there has been no consensus on whether either or both scales should be used.

In routine clinical practice, Shuttleworth *et al.* (1990) found in an audit of 100 psoriasis consultations that the majority of case notes lacked an assessment of extent or distribution of lesions, or any reference to the patient's symptoms or disability. However, it was difficult to determine whether it was the patient's or the clinician's evaluation of treatment which was recorded at the follow-up visit. In the absence of any baseline measurements, it would be difficult to compare the outcomes relating to different treatments.

Efficacy of antipsoriatic treatments are often only evaluated in terms of clearing capacity. However, the duration of the post-treatment remission has been recognised as a major importance to patients (van de Kerkhof 1997).

Vardy *et al.* (1993) proposed the following score:

$$\text{response to treatment} = \frac{\text{(Number of weeks of intensive therapy needed to induce remission)}}{\text{(Number of months after treatment during which the patient is in remission)}}$$

The method's simplicity is appealing and it may be more useful for comparing treatments than for providing meaningful absolute estimates of efficacy.

Moreover, additional studies are needed to examine the reliability and validity of such scores before their wider adoption.

2.3.1 Body surface area (BSA)

Many methods of assessment of severity of psoriasis incorporate an estimation of involved surface area. The area of one side of a flat closed hand has been used to represent 1% of the total BSA to estimate the extent of skin involvement in patients with psoriasis (Stern *et al.* 1986). However, this technique is likely to overestimate the true value. Planimetric investigations have suggested that a hand area actually represents 0.70-0.76% of BSA (Long *et al.* 1992). The rule of nines method assumes that the total BSA comprises head (9%), anterior trunk (upper 9%, lower 9%), posterior trunk (upper 9%, lower 9%), each leg (anterior 9%, posterior 9%), each arm (9%), and the genitalia (1%). However, using the rule of nines, untrained observers overestimate the extent of psoriatic lesions, particularly when assessing small plaque psoriasis (Ramsay & Lawrence 1991). Other studies using schematic outlines of the human form have yielded similar results (Tiling-Grosse & Rees 1993).

There is high interobserver variability in the calculation of BSA among clinicians (Marks *et al.* 1989, Ramsay & Lawrence 1991, Tiling-Grosse & Rees 1993), an important concern in multi-centre trials. In a study of 10 patients with chronic plaque psoriasis, four clinicians significantly differed in their rank ordering of skin involvement ($p \leq 0.001$, Friedman nonparametric ANOVA) (Marks *et al.* 1989). Over a two-day period, Ramsay & Lawrence

(1991) examined the test-retest reliability of four untrained observers estimation of involved BSA in 10 patients. Individual observer's scores varied between 1% and 2% which were not significant, suggesting that sequential estimates made by the same observer are consistent. However, observer bias may have been introduced by the clinicians' recollection of their previous BSA assignment. Plaque tracing (Ramsay & Lawrence 1991) and point counting grids (Bahmer 1989) have been reported to improve accuracy. However, these techniques have not been rigorously validated. Computer image analysis (CIA) has been developed to provide objective quantitative data on the extent of psoriasis (Marks *et al.* 1989, Ramsay & Lawrence 1991, Savolainen *et al.* 1997). Unfortunately, CIA is not effective over curved body sites (Savolainen *et al.* 1997, Ormerod *et al.* 1997). Like many objective measures, this procedure is also expensive, time consuming, and lacks practicality for use in large-scale clinical trials or routine patient follow-up (Savolainen *et al.* 1997).

2.3.2 Erythema, Induration and Desquamation

Visual assessments of these physical signs have not been as thoroughly investigated as BSA measurements. However, a 2 week bilateral comparative trial of betamethasone valerate against white soft paraffin (n=12) found that subjective scoring (erythema; plaque elevation; scale; and a composite total) made by a single observer had comparable power to objective measures (CIA;

erythema reflectance; nitric oxide production; ultrasound scan for thickness, scale, and echo-poor zone) (Ormerod *et al.* 1997). Previous studies have also demonstrated that visual gradings of skin erythema correspond with measurements obtained by a laser Doppler flowmeter, a spectroradiometer, an erythema meter and a chromameter (Serup & Agner 1990, Lahti *et al.* 1993).

Attempts have been made to measure scaling using optical profilometry and scanning macrophotographic densitometry, but the reliability, validity and clinical meaning of these techniques remain to be determined (Marks 1996). Plaque thickness has been measured using mechanical calipers (Lawrence *et al.* 1986). However, technical problems include exudation of tissue fluid out of the skin fold during measurement. Alternatively, pulsed A-scan ultrasound has been recommended as the most accurate method to measure the thickness of psoriatic lesions (Marks 1996).

2.3.3 The Psoriasis Area and Severity Index (PASI)

The PASI scoring system assesses four body regions: the head (h), the upper extremities (u), the trunk (t), and the lower extremities (l), corresponding to 10%, 20%, 30%, and 40% of the total BSA, respectively (Fredriksson & Pettersson 1978). The area of psoriatic involvement for each of the four regions is assigned a numerical value (A) of 0 to 6 corresponding to 0% to 100% involvement: 0 = no involvement, 1 = <10%, 2 = 10<30%, 3 = 30<50%,

4 = 50<70%, 5 = 70<90%, 6 = 90-100%. For each region erythema (E), induration (I), and desquamation (D) are rated according to a 5-point scale, where 0 = no involvement, 1 = slight, 2 = moderate, 3 = marked, and 4 = very marked. The PASI score is then calculated from the following formula:

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

The PASI score can vary in increments of 0.1 units from 0.0 to 72.0, with higher scores representing a greater degree of psoriatic severity.

Reliability and validity of the PASI

To have content validity, the PASI must include the primary signs and symptoms of psoriasis related to severity (Exum *et al.* 1996). However, dermatologists' assessment of disease severity and patients' assessment of the same severity of psoriasis can be inconsistent. When dermatologists (n=21) and patients (n=56) ranked a list of fifty features considered characteristic of psoriasis or associated with its course, there was considerable discrepancy between their ratings (Baughman & Sobel 1970). Patients considered "embarrassment over appearance" as most characteristic of severity, while dermatologists assigned it least importance. Moreover, dermatologists ranked "shivering", "fever", and "pustular areas (other than palms and soles)" as very indicative of disease severity, features which are not addressed in the PASI

method.

Criterion validity is restricted by the lack of a “gold standard” measure of psoriatic severity (Exum *et al.* 1996). However, as mentioned previously, a number of objective instrumental techniques have been developed for assessing BSA, erythema, induration, and desquamation, against which subjective ratings by clinicians can be assessed. Research investigating the reliability of the PASI has focussed mainly on the clinicians’ assessment of affected BSA. Additional research is required to explore the reliability of the assessments for erythema, desquamation, and induration, together with overall PASI scores (Exum *et al.* 1996).

Limitations of the PASI

By far, the greatest drawback of the PASI is its lack of sensitivity (Marks 1996). Erythema, desquamation and induration are scored with equal weight within each of the four body regions. Thus, a reduction in scaling with a concomitant increase in skin erythema could be recorded with the same PASI score. Similarly, a case of psoriatic erythroderma with moderate erythema, slight induration and scaling could have an identical score as a patient with chronic plaque psoriasis involving 10-30% of BSA, but with marked erythema, induration and desquamation (van de Kerkhof 1992). Whereas the former condition is particularly severe and difficult to treat, the latter usually responds to many forms of treatment (Bigby & Gadenne 1996). Attempts have

been made to improve the sensitivity of the PASI. Saurat *et al.* (1988) increased the number of body regions evaluated to eighteen, but this modified index failed to detect a significant difference between an etretinate-PUVA combination and a placebo-PUVA combination.

Despite its widespread use, limited attention has been paid to the clinical relevance of derived PASI scores. For example, a change in score from 38 to 32 may be statistically significant, but the clinical significance may not always be apparent. Similarly, does a change from 48 to 38 correspond to a change from 28 to 18? Until these properties have been fully examined, such measurements should be interpreted with suspicion. In practice, PASI scores greater than 40 are rare, such that almost half the range is redundant (Logan 1994). Several effective treatments, such as dithranol, can also produce marked erythema which may significantly influence the PASI score (van de Kerkhof 1992). Moreover, erythema and scaling can fluctuate rapidly with changes in temperature, humidity and the recent application of emollients.

2.3.4 Patient measurement of the PASI

The self-administered psoriasis area and severity index (SAPASI) is a structured instrument consisting of a silhouette of a body for patients to shade in the affected areas and of three visual analogue scales for recording the erythema, induration, and scaliness of an average lesion (Fleischer *et al.*

1994). Recent research has focussed on examining its reliability and validity (Feldman *et al.* 1996). In 19 patients, the test-retest reliability was investigated over a two day period ($r=0.82$, $p=0.0001$). Despite the lack of a “gold standard”, SAPASI measurements were compared against PASI scores ($r^2=0.59$, $p=0.0001$) in an attempt to evaluate the criterion validity ($n=80$). However, a plot of the difference between the scores against their mean value would have proved more informative, thereby examining the level of agreement between the two instruments. Additional research is required to fully evaluate the psychometric properties of the SAPASI, which may serve as a means by which patients can evaluate the physical characteristics of their psoriasis in future trials.

2.3.5 Dermatology Index of Disease Severity (DIDS)

The DIDS focusses on two factors, the percentage of involved BSA and functional limitation, in forming a 5-stage scale ranging from stage 0 to stage IV: 0, no evidence of clinical disease; I, limited disease; II, mild disease; III, moderate disease; and IV, severe disease (Faust *et al.* 1997). The degree of interobserver concordance has been measured in 34 psoriasis patients with the Cohen κ statistic. The number of raters varied from 3 to 10 and the overall κ statistic was 0.76, which, in line with generally accepted criteria, was defined as "substantial agreement". Examination of the construct validity compared DIDS and PASI ratings in 8 patients with psoriasis. A recent editorial,

however, outlined a number of potential limitations with the DIDS in dermatologic health services research (Williams 1997). Further studies are needed to determine to what extent a scale restricted to grading BSA and functional disability is appropriate for grading psoriatic severity together with a comprehensive evaluation of the psychometric properties of such a scale. A summary of the testing of the properties of the various clinical outcome measures used in psoriasis is shown in Table 2.2.

Table 2.2 : Summary of the psychometric testing of clinical outcome measures in psoriasis. (NR : not reported)

Outcome	Reliability			Validity		Construct
	Test-retest	Interobserver	Content	Criterion		
Body Surface Area affected	Using the rule of nines, differences of just 1-2% over 1 day interval ($p > 0.05$, ANOVA) for 4 untrained observers ($n=10$).	High variability in the calculation of BSA among clinicians.	Important indicator to both patients and clinicians.	Poor correspondence between computer image analysis estimates and those made by clinicians. Observers overestimate BSA, particularly when assessing small plaque psoriasis.	Comparison of PASI BSA scores with SAPASI BSA scores.	
Erythema	NR	NR	Indicator of inflammation. Several effective treatments can cause marked erythema.	Good correspondence between visual ratings and those obtained by a laser Doppler flowmeter, a spectroradiometer, an erythema meter and a chromameter.	Comparison of clinical scores with (1) SAPASI, (2) multiparameter flow cytometry results.	
Induration	NR	NR	Most sensitive clinical parameter of disease activity.	Good correlation between visual ratings and those obtained by ultrasound ($n = 12$): $r_s = 0.58$, $p < 0.0005$	Comparison of clinical scores with (1) SAPASI, (2) multiparameter flow cytometry results.	
Desquamation	NR	NR	Ranked by patients ($n = 56$) as very indicative of severity.	Good correlation between visual ratings and those obtained by ultrasound entry echo ($n = 12$): $r_s = 0.53$, $p < 0.0005$	Comparison of clinical scores with (1) SAPASI, (2) multiparameter flow cytometry results.	
PASI	NR	NR	NR	NR	Comparison of PASI with (1) Psoriasis Disability Index, (2) SAPASI, (3) DIDS, (4) various biological markers of disease severity (eg. urinary neopterin levels, IL-2R-positive lymphocytes, sICAM-1, etc.)	
SAPASI	2 day interval ($n = 19$): $r = 0.82$, $p = 0.0001$	ICC = 0.953 for BSA estimates among 5 raters	NR	NR	Comparison of SAPASI with (1) PASI, (2) global severity scores, (3) erythema, scale and induration scores	
DIDS	NR	Cohen κ statistic = 0.76 for 3 to 10 raters ($n=34$)	NR	NR	Comparison of DIDS and PASI rating in 8 psoriasis patients.	

2.4 Conclusions

In clinical trials of psoriasis treatment, outcomes are often measured using scales of unknown reliability and validity. One of the potential dangers is that uncritical use of outcome measures could lead to inaccurate or inappropriate data. The development of a reliable and validated measure that is easy to use and responsive to clinically significant changes is urgently required.

Further research is needed to determine the most appropriate and sensitive parameters when measuring drug efficacy in psoriasis. Physical signs such as erythema, induration and desquamation are important in assessing the severity of the disease and reproducible readings can now be obtained using instrumental methods for measuring physical changes such as erythema. The major problem is how to weight the different signs of the disease to have a summary score, which reflects the severity of the disease meaningfully for the patient and clinician. It is obvious that for each of the signs, the relationship between score and severity is not necessarily linear and existing scales, including the PASI, assume that they are. Moreover, the scales also assume equal weights for the different signs. With the necessary calibration of instrumental or summary score against disease severity, the former can then be used routinely and at lower cost for comparing relative efficacy of competing treatments. Moreover, with clinically-calibrated instrumental methods, fewer patients would be required because of the improved study power achievable with the more precise instrumental methods.

Equally important is the need to standardise outcome measures, thereby enabling direct comparisons to be made between clinical trials. For systemic or total body treatments, time to clearance or relapse would be useful clinical outcome measures to use. However, the definition of clearance or relapse would need to be precisely defined and universally agreed on so that the results of different clinical trials can be directly compared. Likewise, the proportion of patients achieving moderate or marked improvement at a given assessment point is useful but again, precise definitions of those adjectival descriptors is essential. Such outcomes are particularly important if they are to be used for cost-effectiveness studies. Among other chronic diseases, for example rheumatoid arthritis, recent international efforts have resulted in recommendations for use of a minimum core set of outcome measures in all clinical trials (Felson 1993).

More appropriate statistical methods may also play an important part in the interpretation of results, whatever the inadequacies of the rating scales used. There is room for improvement in the methods of analysis of both response and relapse data. Clinical trials which measure the difference in response for a given parameter between study entry and completion do not take into account serial data or disease fluctuations. A possible alternative approach is to use the area under a response-time curve (AUC) as a summary measure which captures changes in disease status over the whole study (Liu *et al.* 1998).

CHAPTER 3

Quality of life measures : a critical appraisal of their quality

3.1 Introduction

In recent years, the importance of patient-generated evaluations in assessing the impact of healthcare has been recognised. A plethora of quality of life (QoL) instruments have been developed to measure the burden of psoriasis and its treatment on the patient. This chapter reports on the QoL measures and provides a critical appraisal of their quality.

3.2 Quality of Life

The World Health Organisation (WHO) defined health as “a state of complete physical, mental and social well-being” (World Health Organisation 1958).

Quality of life (QoL) is a multidimensional concept encompassing the physical, social, and emotional well-being of a person (McKenna & Stern 1996). Since many factors influence an individual's QoL, the term health-related quality of life (HRQoL) is more narrowly defined, relating to the disease process or its treatment.

In the absence of a permanent cure, the goal of treatment is to minimise the

extent and severity of psoriasis to the point at which it no longer disrupts substantially the patient's QoL (Gawkrodger *et al.* 1997). Traditionally, clinical assessments of psoriatic severity incorporated a physician's rating of different skin signs. These techniques, however, do not quantify the effect of psoriasis on patients' lives or the manner in which treatment improves HRQoL. For example, two patients with the same clinical rating may have dramatically different QoL outcomes, highlighting the importance of issues such as role function and emotional well-being.

The impact of psoriasis on patients is profound and can cause considerable morbidity (Ramsay & O'Reagan 1988, McHenry & Doherty 1992, Fried *et al.* 1995, McKenna & Stern 1997, Rapp *et al.* 1997). Many patients experience problems with body-image, self-esteem and self-concept, poor psychological adaptation, and feelings of stigmatisation, shame and embarrassment concerning their appearance (Jowett & Ryan 1985, Ramsay & O'Reagan 1988, Ginsburg & Link 1989, Nevitt & Hutchinson 1996). Several attempts have been made to quantify psychological stress in psoriasis patients. Gupta & Gupta (1995) developed the Psoriasis Life Stress Inventory (PLSI), while other groups have designed questionnaires which specifically explore the social and psychological impact of skin conditions (Ginsburg & Link 1989, Wessely & Lewis 1989). In a sample of dermatology outpatients, Wessely and Lewis (1989) used the General Health Questionnaire (12-item version) and an impact of skin disease computer program (IMPACT) to measure the psychological effects of skin disease. IMPACT asked patients specific questions concerning

their appearance, avoidance of social situations, embarrassment and sexual problems. These components are not addressed in the commonly used pooled indexes and this omission may ultimately underestimate the overall impact of psoriasis on the patient (McHenry & Doherty 1992).

3.3 Quality of Life Instruments

Questionnaires designed to measure HRQoL can be categorised into either discriminative or evaluative instruments. The former type is commonly used to differentiate between individuals at a point in time, while the latter type is required to quantify change over a period of time (Guyatt *et al.* 1993). Items may be categorised into several dimensions which may include, for example, physical, emotional, and social function, role performance and pain. Response options are generally standardised. The techniques used have included simple “yes” or “no” choices, visual analogue scales, and graded Likert-type measures (McKenna & Stern 1996). Amongst the QoL instruments, scoring systems can vary considerably. However, the use of complicated weighting schemes may not offer any advantage over simple summation techniques (Fletcher *et al.* 1992). Alternatively, QoL instruments have been classified as either generic, disease-specific or speciality-specific.

Generic measures are designed to assess a complete spectrum of dimensions applicable to a variety of health states, conditions and diseases (Testa & Simonson 1996). Several generic health questionnaires have been used in

psoriasis studies, including the United Kingdom Sickness Impact Profile (UKSIP) (Finlay *et al.* 1990, Finlay 1994), the Short-Form 36 (SF-36) Health Survey (Nichol *et al.* 1996, O'Neill 1996), the Nottingham Health Profile (NHP) (Morgan *et al.* 1997), and the General Health Questionnaire (GHQ) (Root *et al.* 1994). This has allowed comparisons to be made across different disease states (Finlay *et al.* 1990). Additional advantages include a greater ability to detect the non-specific effects of treatment (Fletcher *et al.* 1992).

Psoriasis-specific measures focus on the dimensions most relevant to the disease. Consequently, generic instruments may be less responsive to changes in psoriatic severity than either psoriasis or dermatology-specific instruments (Nichol *et al.* 1996). To capture all aspects of psoriasis that impact on HRQoL, the use of a generic measure in conjunction with a psoriasis-specific instrument has previously been recommended (McKenna & Stern 1996, Nichol *et al.* 1996). Alternatively, the Patient Generated Index (PGI) enables patients to select specific elements of life affected by their condition (Ruta *et al.* 1994). This encompasses the impairment attributable to differences in lifestyle among patients with the same disease, such as income, living conditions, and social activities. Herd *et al.* (1997) have used the PGI to determine QoL in a community study of atopic dermatitis. Further studies are needed to ascertain whether such a scale would be useful for assessing the burden of disease severity and outcome of treatments in psoriasis.

3.3.1 Psoriasis Disability Index (PDI)

Finlay & Kelly (1987) developed the PDI after questioning 54 psoriasis patients on functional lifestyle disability caused by psoriasis. The original 10-item instrument demonstrated sensitivity to changes in psoriatic severity following in-patient topical treatment. A modified 15-question version covers five main areas, namely daily activities (five items), work or school (three items), personal relationships (two items), leisure (four items), and treatment (one item) (Finlay *et al.* 1990). The items, which concern the previous month only, are answered either on a 7-point visual analogue scale (Finlay *et al.* 1990) or by a graded 4-point tick-box system (Finlay & Coles 1995). The PDI score is then calculated by summing the scores for each question.

In a study of 340 dermatology out-patients, Kent & Al-Abadie (1993) examined the specificity and internal structure of the 15-item instrument. Three items were found to apply to patients with other skin conditions; the investigators concluded that these items should be removed from the questionnaire if the intention is to determine the effect of psoriasis specifically. Factor analysis of the PDI identified two subscales, one representing various aspects of everyday activities, the other concerning specific public situations (Kent & Al-Abadie 1993). Construct validity has been examined against three generic quality of life instruments: the UK Sickness Impact Profile (UKSIP) were rank-order correlation coefficient, $r_s=0.47$ ($p<0.01$, $n=32$) (Finlay *et al.* 1990); the 28-item General Health

Questionnaire (GHQ) were $r_s=0.71$ ($p<0.001$, $n=22$) (Root *et al.* 1994); and in two studies the SF-36 were Pearson correlation coefficient, $r=-0.17\rightarrow-0.45$ ($p<0.001$, $n=644$) (O'Neill 1996) and $r=-0.29\rightarrow-0.44$ ($p<0.0001$, $n=404$) (Nichol *et al.* 1996) for each scale. PDI scores have also been compared against the PASI were $r_s=0.40$ ($p<0.05$, $n=32$) (Finlay *et al.* 1990). It is important to note, however, that while a significant Pearson or rank-order correlation coefficient shows that two measures correlate it does not define how well a score derived using one scale maps onto another.

3.3.2 The Psoriasis Life Stress Inventory (PLSI)

The PLSI was developed to measure stress associated with the cosmetic disfigurement and social stigma associated with having psoriasis, and coping with the physical aspects of the disease and its treatment (Gupta & Gupta 1995). The 15-item version is primarily based upon the investigators' clinical experience with 50 psoriasis patients, and subsequently modified from the responses obtained from 217 inpatients and outpatients. The patient is asked to rate the level of stress, on a four-point scale, experienced over the previous month with a list of potential psoriasis-related psychosocial problems.

In the preliminary study ($n=217$), the internal consistency for all 15 items was high (Cronbach's $\alpha = 0.90$), and significant Pearson correlations were found between PLSI scores and patient assessments of erythema ($r=0.15$, $p=0.04$), scaling ($r=0.20$, $p=0.008$), plaque thickness ($r=0.17$, $p=0.02$), pruritus ($r=0.24$,

$p=0.001$), and overall severity ($r=0.19$, $p=0.01$) (Gupta & Gupta 1995).

However, a study of 150 psoriasis outpatients found that PLSI scores were independent of clinical severity as assessed by the PASI (Fortune *et al.* 1997).

The deletion of three items also improved the internal consistency of the instrument for use in the UK.

3.3.3 Dermatology Life Quality Index (DLQI)

Finlay & Khan (1994) developed the DLQI after questioning 120 outpatients presenting a wide range of skin conditions. The 10-item questionnaire is designed to provide a simple practical method of measuring the disability experienced by patients with skin disease. Respondents consider the previous seven days and answer questions on a 4-point Likert scale. Scores range from 0 to 3 corresponding to “not at all”, “a little”, “a lot” and “very much”, respectively. The DLQI represents the sum of the scores for each question, ranging from 0 to 30, which may also be expressed as a percentage of the maximum score.

Reliability of the DLQI has been examined using a one week test-retest method in 53 dermatology outpatients ($r_s=0.99$, $p<0.0001$) (Finlay & Khan 1994). Testing of the construct validity included a comparison of scores between 200 dermatology outpatients and 100 control subjects (Finlay & Khan 1994). In a study of patients with mild-to-moderate psoriasis ($n=644$), the DLQI was cross-validated against the PDI ($r=0.82$, $p<0.001$) and the SF-36

($r=-0.13 \rightarrow -0.43$, $p<0.001$) (Nichol *et al.* 1996). In addition, the DLQI has demonstrated sensitivity to changes in life quality following inpatient treatment ($n=181$) (Kurwa & Finlay 1995). The mean DLQI score on admission was 13.2 (SD 7.6) which decreased to 7.7 (SD 6.8, $p<0.001$) four weeks after discharge. In particular, psoriasis patients ($n=63$) improved from 13.7 (SD 6.5) to 6.7 (SD 5.6, $p<0.001$).

3.3.4 The Children's Dermatology Life Quality Index (CDLQI)

Skin disease can have a profound impact on the quality of life of children (Lewis-Jones *et al.* 1996). The CDLQI was developed to quantify the level of impairment (Lewis-Jones & Finlay 1995). This 10-item instrument is based on the responses from 169 children on the ways in which their skin condition affected their lives. Each question addresses the previous week and is answered on a graded 4-point (0-3) scale. The result can be expressed as the sum of the individual question scores or as a percentage of the maximum possible score. Test-retest reliability has been examined in 46 children over a 4-day interval ($r_s = 0.86$, $p<0.0001$) (Lewis-Jones & Finlay 1995). Construct validity testing has included the use of the CDLQI in two control populations (Lewis-Jones & Finlay 1995) and demonstration of improvement in scores following in-patient treatment for psoriasis and atopic dermatitis ($n=15$) and out-patient treatment for acne ($n=15$) (Lewis-Jones *et al.* 1996).

3.3.5 Dermatology Quality of Life Scales (DQOLS)

The DQOLS were designed to complement the DLQI, but place greater emphasis on the psychosocial dimension (Morgan *et al.* 1997). The instrument consists of 41-items comprising psychosocial (17 items), physical activities (12 items) and symptom scales (12 items), derived from the reported burden of skin conditions by 50 dermatology outpatients. Each item is rated on a five-point Likert scale ranging from 0 to 4 (very slightly or not at all, a little, moderately, quite a bit, and extremely) and patients are asked to evaluate their current perceptions to each item.

The internal consistency of the instrument has been evaluated in 118 outpatients; Cronbach's α coefficients of 0.92 for the 17 psychosocial items and 0.83 for the 12 activity items were reported (Morgan *et al.* 1997). Test-retest reliability has been conducted on 41 psoriasis patients undergoing phototherapy treatment, with interclass correlation coefficients of 0.84 for both the psychosocial and activity scales. The mean difference in scores for each patient between the two time periods was 4.41 for the psychosocial scale and 2.85 for the activities scale as determined by the Bland-Altman method (Bland & Altman 1986). Construct validity testing has included the ability of the scales to detect clinically expected differences in psychosocial and activity scores among dermatology patients, with particular reference to psoriasis and acne sufferers. In addition, the DQOLS have been validated against the Nottingham Health Profile (NHP), in which the dermatology-specific

instrument demonstrated greater sensitivity to the burden of acne and psoriasis on patients' QoL (Morgan *et al.* 1997).

3.3.6 Skindex

Skindex was developed to comprehensively measure the effects of skin disease on patients' HRQoL (Chren *et al.* 1996). The original 61-item instrument consists of eight scales and the content validity is based on literature review and constructs reported from clinicians and patients. Each item is scored against the patient's perception during the previous four week period. Initially, the internal and test-retest reliability were evaluated in 201 dermatology patients; Cronbach's $\alpha=0.76-0.86$ for each scale and Pearson's correlation coefficients ranged from 0.68 to 0.90 after 72 hours (Chren *et al.* 1996).

Construct validity has been examined in a comparison between patients with inflammatory skin conditions and those with isolated lesions. Patients afflicted with inflammatory conditions achieved higher scale scores as predicted (Chren *et al.* 1996). Factor analysis identified seven underlying factors, accounting for 78% of the variance, which correlated with the scale scores of Skindex (Chren *et al.* 1996). Convergent and discriminant validity have been examined against the SF-36 (Chren *et al.* 1997a). For convergent validity, scatter plots of patients' scores on similar scales in the two instruments were examined and Pearson correlation coefficients calculated

between the scales. With discriminant validity, Spearman rank-order correlations of SF-36 and Skindex comparative scale scores were compared with patients' responses about general health and skin-specific traits.

Attempts have been made to improve the discriminative and evaluative capacity of the instrument. Recently, the reliability and validity of a refined 29-item version of Skindex has been explored in 692 dermatology outpatients (Chren *et al.* 1997b). Cronbach's $\alpha=0.87-0.96$ for each scale, and patients with psoriasis and eczema responded with higher scores than patients with isolated lesions, as predicted. Exploratory factor analysis found that 97% of the variance was explained by three factors which correlated with the *a priori* scales. Specifically, the scale scores shifted in the expected direction in patients who reported that their skin condition had changed after three months. In addition, the test-retest reliability was determined in 105 patients after 72 hours ($r=0.88-0.92$) with an average time of 5 minutes to complete the revised version compared with 15 minutes for the original instrument. A summary of the psychometric properties of QoL instruments used in psoriasis is shown in Table 3.1.

Table 3.1 : Summary of the psychometric testing of QOL instruments used in psoriasis. (NR: not reported)

Instrument	Influential factors	Reliability		Validity		Construct
		Internal consistency	Test-retest	Content		
PDI (15 item)	2 factors accounting for 54.8% of variance: (1) various everyday activities, (2) specific public situations	Using Rank correlation test: $0.32 \leq r_s \leq 0.40$ for 10 items when all questions paired.	NR	Literature review, modified from responses of 54 psoriasis patients.		Testing included comparison of PDI scores with (1) psoriasis and other dermatology patients; (2) PASI; (3) UKSIP; (4) 28-item GHQ; (5) patients' self-rated severity; (6) DLQI; and (7) SF-36.
PLSI (15 item)	2 factors accounting for 56.2% and 11.8% of the variance, respectively: (1) anticipatory/avoidance stress, (2) experiences of rejection.	In US, $\alpha=0.90$ for all 15 items (n=217). In UK, $\alpha=0.88$ for all 15 items (n=150).	NR	Based on clinical experience with 50 psoriasis patients, modified from the responses of 217 inpatients and outpatients.		Testing included comparison of PLSI scores with global patient ratings of psoriatic severity. PLSI score of ≥ 10 delineated patients with greater overall severity ($p=0.007$), more cosmetically disfiguring psoriasis ($p<0.01$), greater number of flare-ups of psoriasis ($p=0.009$) and greater pruritus severity ($p=0.001$).
CDLQI	NR	NR	4 day-interval (n=46): $r_s=0.86$, $p<0.001$	169 children reported on how their skin disease affected their lives.		Comparison of CDLQI scores between 233 dermatology paediatric outpatients, 47 normal controls and 55 control patients attending a general paediatric clinic.
DLQI	NR	Using rank correlation test, $r_s=0.23 \rightarrow 0.70$, $p<0.002$ when all questions paired.	1 week-interval (n=3): $r_s=0.99$, $p<0.0001$	120 outpatients reported on how their skin disease affected their lives.		Testing included comparison of DLQI scores with (1) 200 dermatology outpatients and 100 control subjects; (2) PDI; and (3) SF-36.
DQOLS	4 psychosocial scales: embarrassment, despair, irritableness, distress 4 activity scales: everyday, summer, social, sexual	$\alpha=0.92$ for 17 psychosocial items; $\alpha=0.83$ for 12 activity items (n=118)	7-10 day-interval (n=41): ICC=0.84 for psychosocial and activity scales	50 outpatients reported on how their skin condition affected their lives.		Detection of clinically expected differences in psychosocial and activity scores among dermatology patients. Cross-validation against the NHP, in which the DQOLS demonstrated greater sensitivity to the burden of acne and psoriasis on patients' HRQoL.
Skindex (29-item)	3 factors accounting for 97% of variance: emotions, symptoms, functioning	$\alpha=0.87 \rightarrow 0.96$ for each scale (n=692)	3 day-interval (n=105): $r=0.88 \rightarrow 0.92$ for scale scores	Literature review and constructs reported from clinicians and patients		Testing included (1) comparison of scores in patients with psoriasis and eczema, with patients with isolated lesions; (2) exploratory factor analysis identified 3 underlying factors which correlated with the <i>a priori</i> scales; (3) comparison of Skindex scores and clinical severity as judged by clinicians.

3.4 Problems with quality of life

Despite the proliferation in the number of QoL instruments in recent years, confusion still remains about how quality of life should be measured (Muldoon *et al.* 1998). Instruments differ in how they have been constructed, the categories and items included, and the methods by which their reliability and validity have been examined. Consequently, we are faced with the task of selecting a suitable instrument from a range of competing alternatives which may ultimately yield different results. The way in which patients evaluate their quality of life may also change over time. For example, newly diagnosed patients with chronic conditions, including dermatologic disorders, have been shown to have higher mental health scores than patients who had been living with their illness for longer periods (Cassileth *et al.* 1984). Therefore, improvements in QoL scores over time, may not necessarily represent actual changes in health or symptoms, but reflect psychological adaptation (Muldoon *et al.* 1998). Additional work is needed to interpret the meaning of a given amount of change in QoL scores in relation to the patient's perception of their improvement or deterioration (Juniper *et al.* 1994).

With the move towards using QoL instruments in international multicentre trials, cross-cultural issues need to be considered. Previous studies have shown that cultural factors can influence the type of activities engaged in by individuals, including preferred ways of spending time and the relative values placed on these activities and on health, physical strength and relationships

(Leplège & Hunt 1997). In particular, Koo (1996) has already argued that the PDI may not be an appropriate instrument to use on the typical psoriasis patient in the United States.

3.5 Utility measures

Utility measures of quality of life are quantitative expressions of preference for potential health states (Zug *et al.* 1995). Typically, the utility approach yields a single index value, usually between 0 (death) and 1 (perfect health), which represents the HRQoL of the individual at a particular point in time (Torrance 1987). The quality adjusted life year (QALY) combines in a single number both the quantity of life and its health-related quality. QALYs are calculated by estimating the life years gained from an intervention and weighting each year to account for morbidity. This measure can potentially be utilised in resource allocation decisions, allowing cost-utility comparisons to be made between a wide range of health care interventions. However, as yet there has been little application of QALYs in published dermatological research.

Leu (1985) developed a MIMIC-DISABILITY index described as a one-dimensional measure of the overall psoriasis-related impairment in life quality. The author has described how the index can be incorporated into economic evaluations of new treatments. Using utility assessments, Finlay & Coles (1995) examined the effect of psoriasis on the quality of life of 369

patients. Values were expressed in terms of personal expenditure, time trade-off and comparison with other chronic conditions. In addition to time trade-off, vertical rating scales and standard gamble methodology have been used in assessing patients' decisions concerning methotrexate therapy in psoriasis (Zug *et al.* 1995). Standard gamble involves a paired comparison in which the patient must choose between two alternatives. One alternative has a certain outcome and one alternative involves a gamble with two possible outcomes: the best health state with probability p , or the worst health state with probability $1-p$. Probability p is varied until the patient is indifferent between the two alternatives, at which point the required utility value for the health state can be calculated. Similarly, time trade-off involves a paired comparison of two alternative options. Finlay & Coles (1995) examined the length of time that patients would be prepared to spend on treating their psoriatic lesions each day if this could result in normal skin. Alternatively, patients may be asked to choose between living with psoriasis for the remainder of their lives or selecting a shorter length of life in perfect health (Zug *et al.* 1995).

3.6 Conclusions

Increasingly, there has been a move towards incorporation of patient-generated evaluations when assessing the impact of healthcare. In recent years, a number of QoL instruments have been developed which facilitate a wider examination of the burden of psoriasis and the effects of treatment on the patient. However, there is considerable variation in how the instruments

have been constructed, the categories and items included, and the methods by which their reliability and validity have been examined. In order to guide investigators in their choice of instrument, further head-to-head comparisons of measures should be undertaken. When QoL measures are compared, a Pearson or rank-order correlation coefficient is not sufficient to indicate agreement. Methods that examine agreement, rather than association, are available and should be used. In the future, we will need to demonstrate whether these measurement tools are ready for widespread implementation in clinical trials or routine patient follow-up.

CHAPTER 4

Systematic review of the comparative efficacy and tolerability of calcipotriol

4.1 Introduction

Dermatologists and general practitioners are faced with an increasing choice of antipsoriatic agents to prescribe. In recent years, calcipotriol, has become one of the most widely prescribed topical therapies for psoriasis in the UK. Traditionally, other topical agents including coal tar, dithranol and topical corticosteroids have been the mainstay of treatment for mild-to-moderate psoriasis. However, relatively little is known about their comparative efficacy or tolerability. In order to address these problems, there is a need to systematically evaluate the benefits and risks attributable to the various treatment options. Thus, this chapter provides a systematic review of randomised controlled trials of topical calcipotriol in the treatment of mild-to-moderate chronic plaque psoriasis.

4.2 Methods

4.2.1 Inclusion and exclusion criteria

The following selection criteria were used to identify studies for the analysis:

Types of studies - Only RCTs of calcipotriol were included. A randomised trial was defined as one in which the investigators reported it as randomised without necessarily defining the randomisation procedure explicitly. If a clearly non-random method (for example, dates of birth or sequential assignment) was used, the trial would have been excluded. No trial fell into this category.

Types of participants - Adults or children with chronic plaque psoriasis were eligible for inclusion. Exclusion criteria included guttate, pustular, or erythrodermic psoriasis or psoriasis predominantly located on the face or scalp.

Types of intervention - Calcipotriol 0.005% cream or ointment formulations were considered. Trials in which the same psoriatic lesions were treated only with calcipotriol in combination with another antipsoriatic agent were excluded.

Types of outcome measures - The primary efficacy criteria were the proportion of patients showing marked improvement or cleared in the patients' overall assessments and the mean percentage change from baseline in PASI scores. A modified PASI method was used in the calcipotriol trials in which the head was excluded from the assessment. The resultant score could range from 0.0 to 64.8. The proportion of patients graded as marked improvement or cleared in the investigators' overall assessments of response were used as a secondary outcome measure. Adverse events were also recorded in terms of lesional/perilesional irritation, facial/scalp irritation, exacerbation of psoriasis, and the number of withdrawals due to adverse effects.

4.2.2 Search strategy for identification of studies

Reports of RCTs were identified through a systematic electronic search (from 1987) of Medline, Embase, the Cochrane Controlled Trials Register, and BIDS Index to Scientific and Technical Proceedings. Textwords applied to the search included calcipotriol, MC903, calcipotriene, Dovonex, Daivonex and Psorcutan. The search was most recently updated in October 1998. This was supplemented by searching the reference lists of all retrieved RCTs, review articles, textbooks, and contacting the manufacturer of calcipotriol. Abstracts were considered; relevant information not included in the published reports was obtained by either contacting the principal author of the trial or the manufacturer.

4.2.3 Methods of the review

Separate comparisons were made between calcipotriol and placebo, and calcipotriol and each of several alternative interventions. For efficacy, the results obtained during a treatment period ranging from 6 to 12 weeks are reported. The topical corticosteroids have been grouped based on their potencies: moderate (clobetasone butyrate 0.05%); potent (betamethasone valerate 0.1%, betamethasone dipropionate 0.1%, desoxymethasone 0.25%, fluocinonide 0.05%, halobetasol 0.05%); and very potent (clobetasol propionate 0.05%, diflorasone diacetate 0.05%).

Dichotomous outcomes - Efficacy was estimated with the rate ratio (RR), defined as the proportion of patients achieving at least marked improvement in the calcipotriol group relative to the control group. Adverse effects were also estimated with the RR, the rate difference (RD) and the number needed to treat (NNT) in terms of lesional/perilesional irritation, facial irritation, exacerbation of psoriasis, and the number of dropouts due to adverse effects. The denominator was taken as the number of patients randomised - that is, an intention to treat analysis. In all cases, Rothman's (1986) method was used for interval estimation of the individual RR and RD.

Continuous outcomes - The mean difference in effect (d_i) and 95% confidence interval (CI) were calculated for each trial. Standard errors (SE) were abstracted from the individual studies. When the SEs or SDs and sample sizes

were not provided or could not be calculated on the basis of the data reported, the pooled interstudy SE from studies reporting variances was used (Li Wan Po & Zhang 1997). In estimating the weighted pooled difference in effect (d), the inverse of the squared SE (sampling variance) of the difference in response was used as the weight (ω_i). For interval estimation and calculation of the 95% CI of the pooled estimates, DerSimonian & Laird's (1986) method, as implemented by Whitehead & Whitehead (1991), was used.

Heterogeneity between trials was examined by using χ^2 tests, with $p \leq 0.05$ indicating significant heterogeneity. Provided no significant heterogeneity was identified, summary estimates for the effect from each trial were pooled using a fixed effects model. A random effects model was used if $p \leq 0.05$ for the test for heterogeneity. Results of fixed or random effects modelling are shown when appropriate in the tables and graphs.

Sensitivity analyses were performed by inclusion and exclusion of trials as some characteristics of the interventions varied between trials. Firstly, the results from the intention-to-treat analysis were compared with those obtained if only the remaining patients in the trials were considered. The effect of pooling the results for efficacy in adults and children from the placebo-controlled trials was also examined. Finally, one trial in which patients received once-daily calciprotiol was excluded to examine whether this had a significant impact on the overall estimate of effect.

4.3 Results

Sixty-two reports of RCTs were identified (see Appendix I), of which 37 were included in the analysis (Table 4.1). Of the remaining 25, 12 duplicated results from reports already included while 8 trials failed to meet the inclusion criteria for the following reasons: 4 non-relevant outcomes (Bourke *et al.* 1993, Berardesca *et al.* 1994, Baadsgaard *et al.* 1995, Austad 1997), 3 different concentration/regimen (Kragballe *et al.* 1988, Staberg *et al.* 1989, Schwartzel *et al.* 1996), and 1 scalp psoriasis (Köse 1997). A further 5 reports were excluded for the following reasons: 4 abstracts for which the necessary patient data could not be obtained (Mallett *et al.* 1990, Arevalo & Vega-Lopez 1995, Katz *et al.* 1996, Munro *et al.* 1996); and 1 trial report due to insufficient primary data to conduct the analysis (van de Vleuten *et al.* 1995). In all cases, attempts had been made to obtain the data by contacting the principal author of the trial and the manufacturer.

Table 4.1 : Characteristics of randomised controlled trials.

Trial	Design	Interventions		Duration of follow up (weeks)	No. randomised		Outcome measures (efficacy)		
		CPT	Control		CPT	Control	PASI	IOA	POA
Kragballe 1989	DB-B	0.005% oint. bid	vehicle oint. bid	8	10	10	NR	✓	NR
Dubertret 1992	DB-B	0.005% oint. bid	vehicle oint. bid	2, 4	65	65	✓	✓	✓
Highton 1995	DB-P	0.005% oint. bid	vehicle oint. bid	1, 2, 4, 6, 8	139	138	NR	✓	NR
Guzzo 1996	DB-P	0.005% oint. bid	vehicle oint. bid	1, 2, 4, 8	38	40	NR	✓	NR
Harrington 1996	DB-P†	0.005% cream bid	vehicle cream bid	8	161	87	✓	NR	✓
Oranje 1997	DB-P	0.005% oint. bid	vehicle oint. bid	2, 4, 6, 8	43	34	✓	✓	✓
Pariser 1996	DB-P	0.005% oint. od	vehicle oint. od	1, 2, 4, 6, 8	118	117	NR	✓	NR
Kang 1998	DB-P	0.005% oint. bid	vehicle oint. bid	6	15	15	NR	✓	NR
Kragballe 1991	DB-B	0.005% oint. bid	0.1% BV oint. bid	2, 4, 6	345	345	✓	NR	✓
Cunliffe 1992	DB-P	0.005% oint. bid	0.1% BV oint. bid	2, 4, 6	205	204	✓	NR	✓
Vladimirov 1994	DB-P	0.005% oint. bid	0.1% BV oint. bid	6	32	28	✓	NR	NR
Molin 1997	DB-P	0.005% cream bid	0.1% BV cream bid	4, 8	210	211	✓	✓	✓
Kragballe 1998	DB-P‡	0.005% cream bid	0.005% cream mane + 0.05% CB cream nocte	2,4,8	174	175	✓	✓	✓
Ortonne 1994	DB-P	0.005% oint. bid	0.005% CPT oint. mane + 0.1% BD oint. nocte	1, 2, 4, 6	97	91	✓	✓	NR
Ruzicka 1998	DB-P	0.005% oint. bid	0.005% CPT oint. mane + 0.1% BV oint. nocte	2, 4	87	82	✓	✓	NR
Kragballe 1998	DB-P‡	0.005% cream bid	0.005% cream mane + 0.05% BV cream nocte	2,4,8	174	176	✓	✓	✓
Landi 1993a	DB-P	0.005% oint. bid	0.05% CP oint. bid	2, 4, 6	20	20	✓	NR	NR
Landi 1993b	Open-P	0.005% oint. bid	0.05% CP oint. bid	2, 4, 6	60	60	✓	NR	NR
Medansky 1996	DB-B	0.005% oint. bid	0.05% DD oint. bid	3	134	134	NR	✓	NR
Kim 1994	DB-B	0.005% oint. bid	0.25% DM oint. bid	2, 4, 6, 8	10	10	✓	NR	NR
Lebwohl 1996	DB-P†	0.005% oint. bid	0.05% HB oint. bid	2	42	43	NR	✓	NR
Lebwohl 1996	DB-P†	0.005% oint. bid	0.005% CPT oint. mane + 0.05% HB oint. nocte	2	42	42	NR	✓	NR
Bruce 1994	DB-P	0.005% oint. bid	0.05% FC oint. bid	2, 4, 6	57	56	NR	✓	NR
Crosti 1997	DB-P	0.005% oint. bid	BD + 3% salicylic acid bid	6	80	80	✓	✓	NR
Baiocchi 1997	Open-B	0.005% oint. bid	0.005% oint. od	8	132	132	✓	NR	NR
Kragballe 1998	DB-P‡	0.005% cream bid	0.005% cream od	2, 4, 8	174	174	✓	✓	✓
Meyrat 1996	Open-P	0.005% oint. bid	0.005% CPT cream mane, 0.005% oint. nocte	3, 6	45	46	✓	NR	NR

Table 4.1(cont.) : Characteristics of randomised controlled trials.

Trial	Design	Interventions		Duration of follow up (weeks)	No. randomised		Outcome measures (efficacy)		
		CPT	Control		CPT	Control	PASI	IOA	POA
Bourke 1997a	DB-P	0.005% oint. bid	0.0003% CT oint. bid	1, 2, 4, 6, 8	12	12	✓	NR	NR
de Simone 1993	DB-P	0.005% oint. bid	5% coal cream bid	6	15	15	✓	NR	NR
Tham 1994	SB-B	0.005% oint. bid	WSP mane, coal 15%v/v in aqueous cream nocte	2, 4, 6	30	30	✓	✓	✓
Pinheiro 1997	Open-P	0.005% oint. bid	5% coal tar/ 2% allantoin/ 0.5% HC cream bid	8	69	63	NR	✓	NR
Berth-Jones 1992	Open-P	0.005% oint. bid	0.1-2% DT cream for 30 min od	2, 4, 8	239	239	✓	✓	✓
Grattan 1997	Open-B	0.005% oint. bid	0.1-5% DT gel bid	4	25	25	NR	NR	NR
Lister 1997	SB-P	0.005% oint. bid	1-3% DT cream for 30 min od	8	89	82	NR	NR	NR
Wall 1998	Open-P	0.005% oint. bid	0.1-2% DT cream for 30 min to 1 hr od	12	161	144	NR	✓	✓
Veien 1997	DB-P	0.005% oint. bid	0.0004% TC oint. od	8	145	142	NR	✓	✓
Kragballe 1990	Open-B	0.005% oint. bid	0.005% CPT oint. bid + UVB 3 times weekly	8	20	20	NR	✓	NR
Kersher 1994	Open-B	0.005% oint. bid	0.005% CPT oint. bid + UVB 5 times weekly	2	20	20	✓	NR	NR
Molin 1993	Open-B	0.005% oint. bid	0.005% CPT oint. bid + UVB 3 times weekly	2, 4, 6, 8	101	101	✓	✓	✓
Bourke 1997b	Open-P†	0.005% oint. 100g/week	0.005% CPT oint. 100g/week + UVB 3 times weekly	2, 4	10	10	✓	NR	NR
Bourke 1997b	Open-P‡	0.005% oint. 100g/week	UVB 3 times weekly	2, 4	10	10	✓	NR	NR

† 3-armed head-to-head comparison; ‡ 4-armed head-to-head comparison.

IOA: Investigators' overall assessment; POA: Patients' overall assessment.

DB-P: double-blind, parallel group; DB-B: double-blind, bilateral comparison; SB: single-blind;

CPT: calcipotriol; BV: betamethasone valerate; BD: betamethasone dipropionate; CB:

clobetasone butyrate; CP: clobetasol propionate; DD: diflorasone diacetate; DM:

desoxymethasone; HB: halobetasol; FC: fluocinonide; CT: calcitriol; coal: coal tar; HC:

hydrocortisone; DT: dithranol; TC: tacalcitol.

NR: not reported

4.3.1 Characteristics of eligible trials

In all, 37 eligible trials were retrieved which represented 6038 patients randomised to treatment: 8 were placebo-controlled and 29 included an active comparator. One trial was a four-armed parallel group study while four of the trials were three-armed, head-to-head comparisons; 32 were two-armed, head-to-head comparisons, 11 of which involved a bilateral (right/left) design. The duration of randomised treatment ranged from 2 to 12 weeks. In terms of quality, all trials were randomised and controlled. Eleven trials were open; 2 were single-blind; and 24 were double-blind. Three trials failed to report on the variance of the percentage change in PASI from baseline, necessitating variance imputation (Kersher *et al.* 1994, Vladimirov *et al.* 1994, Ruzicka & Lorenz 1998).

4.3.2 Comparative efficacy of topical calcipotriol

The results of the efficacy analyses are shown in Figures 4.1 to 4.3 and recorded in Tables 4.2 to 4.4.

Figure 4.1: Mean (95% confidence interval) differences in percentage change in PASI from baseline between treatments.

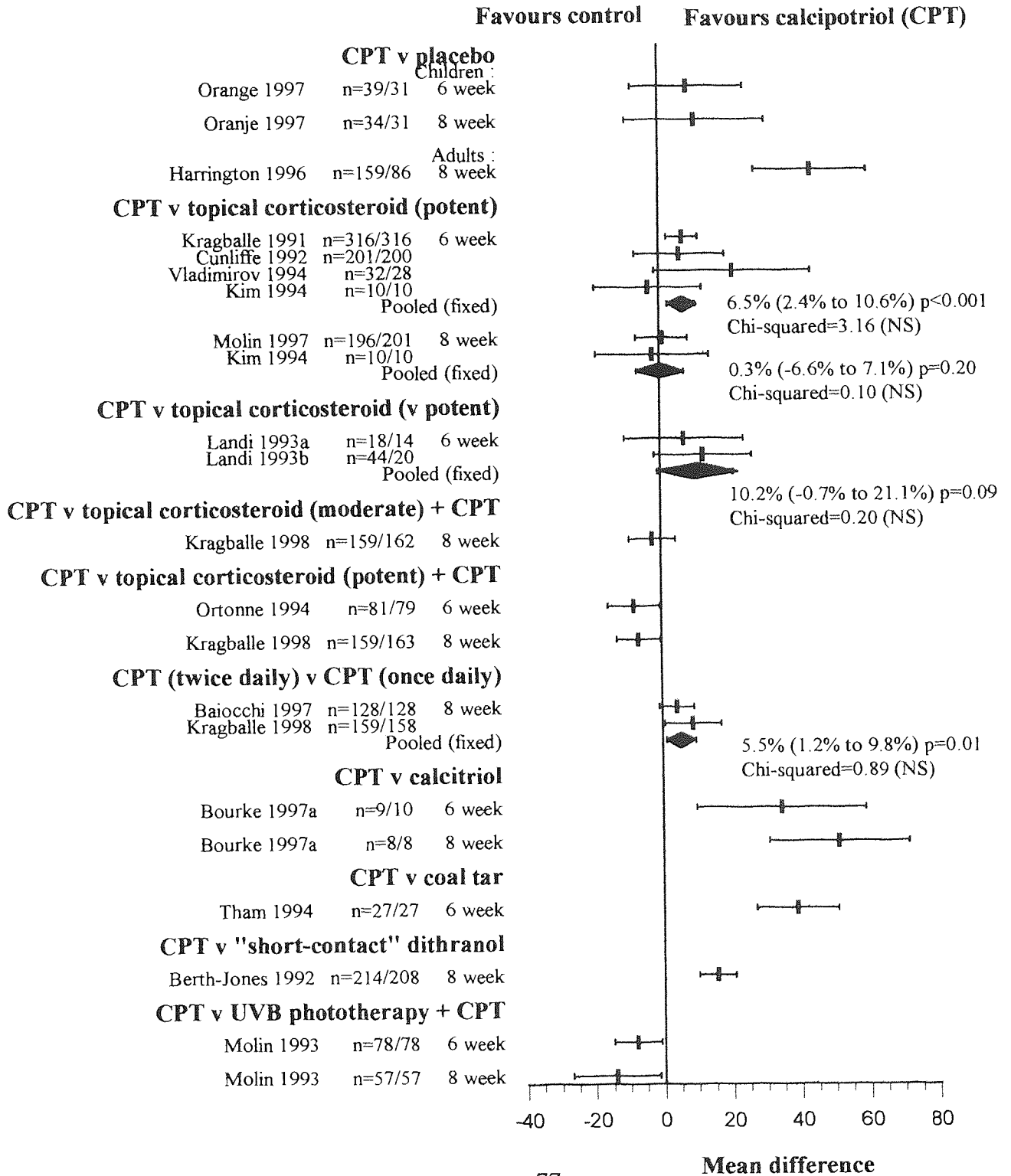


Table 4.2 : Antipsoriatic efficacy (mean difference in percentage change in PASI from baseline, PASI%) between treatments.

Comparison	Treatment duration (weeks)	No. of trials	No. of patients (CPT/ control)	d	SE	Z	PASI%	
							95% CI	χ^2_{heter}
CPT v placebo (children)	6	1	39/31	8.50	8.34	1.02	-7.84, 24.84	/
	8	1	34/31	10.60	10.35	1.02	-9.69, 30.89	/
CPT v placebo (adults)	8	1	159/86	44.10	8.33	5.29	27.77, 60.43	/
CPT v topical corticosteroid (potent)	6	4	559/554	6.50	2.09	3.11	2.41, 10.59	3.16
	8	2	206/211	0.29	3.49	0.08	-6.55, 7.14	0.10
CPT v topical corticosteroid (v potent)	6	2	62/34	10.21	5.57	1.83	-0.71, 21.13	0.23
CPT v topical corticosteroid (moderate) + CPT	8	1	159/162	-2.47	3.47	-0.71	-9.27, 4.33	/
CPT v topical corticosteroid (potent) + CPT	6	1	81/79	-8.00	3.90	-2.05	-15.64, -0.36	/
	8	1	159/163	-6.66	3.28	-2.03	-13.08, -0.24	/
CPT (twice daily) v CPT (once daily)	8	2	287/286	5.47	2.20	2.49	1.16, 9.78	0.88
CPT v calcitriol	6	1	9/10	34.20	12.47	2.74	9.75, 58.65	/
	8	1	8/8	50.90	10.37	4.91	30.57, 71.23	/
CPT v coal tar	6	1	27/27	38.90	6.11	6.37	26.93, 50.87	/
CPT v "short-contact" dithranol	8	1	214/208	15.40	2.69	5.73	10.13, 20.67	/
CPT v UVB phototherapy +CPT	6	1	78/78	-8.00	3.54	-2.26	-14.94, -1.06	/
	8	1	57/57	-14.20	6.51	-2.18	-26.95, -1.45	/

d : mean difference in effect; SE : standard error; z : standard normal statistic; 95%CI : 95% confidence interval

Figure 4.2 : Patient overall assessment: mean (95% confidence interval)

rate ratios for *marked improvement or clearance* between treatments.

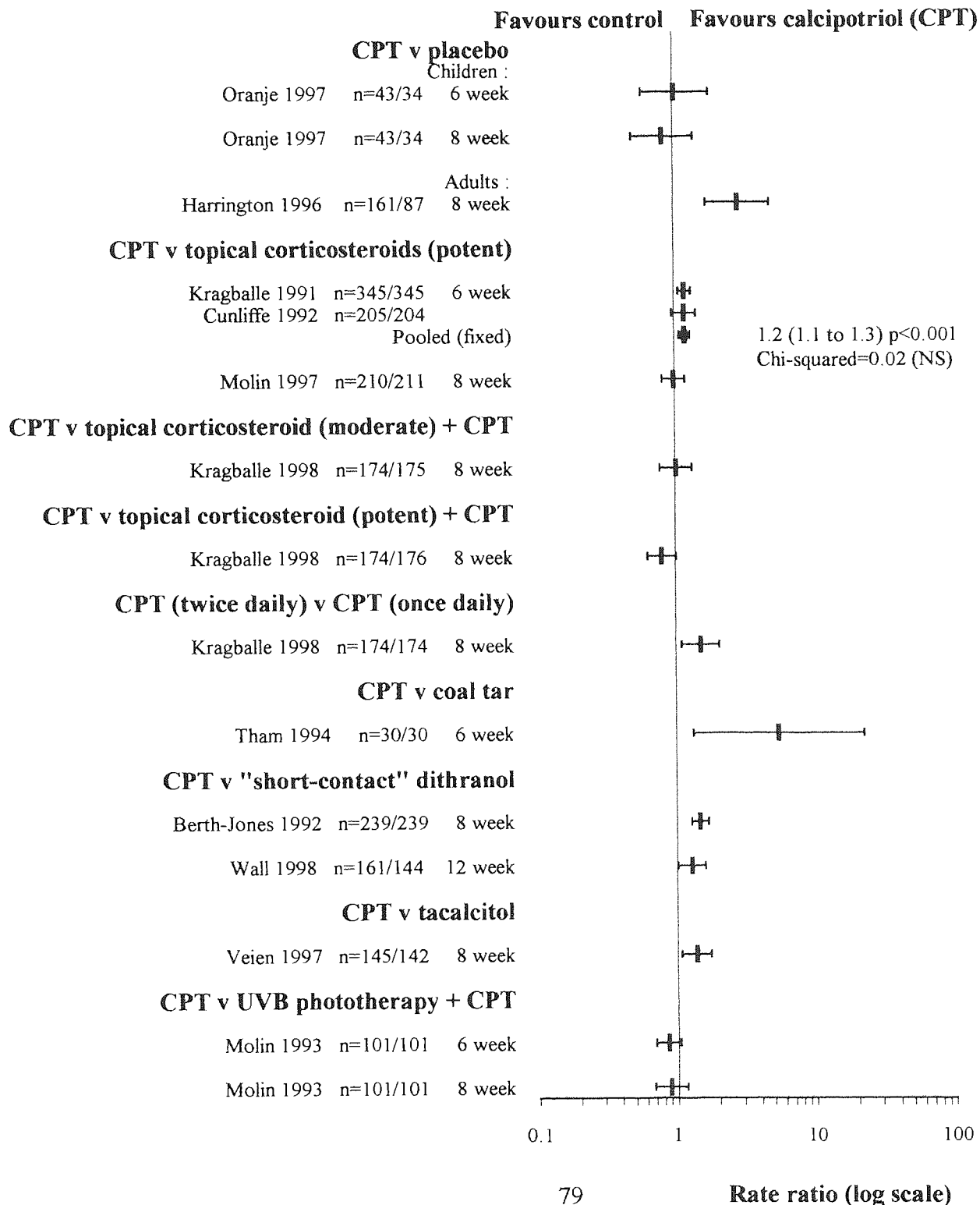


Table 4.3 : Patient overall assessment : Antipsoriatic efficacy (response rate ratio RR) for marked improvement or better between treatments.

Comparison	Treatment duration (weeks)	No. of trials	No. of patients (CPT / control)	lnRR	Response RR				
					SE	Z	χ^2_{heter}	RR	95% CI
CPT v placebo (children)	6	1	43/34	0.03	0.29	0.12	/	1.03	0.59, 1.82
	8	1	43/34	-0.17	0.26	-0.66	/	0.84	0.50, 1.40
CPT v placebo (adults)	8	1	161/87	1.07	0.27	3.94	/	2.91	1.71, 4.95
CPT v topical corticosteroid (potent)	6	2	550/549	0.17	0.05	3.79	0.02	1.19	1.09, 1.30
	8	1	210/211	-0.01	0.10	-0.15	/	0.99	0.82, 1.19
CPT v topical corticosteroid (moderate) + CPT	8	1	174/175	0.02	0.13	0.15	/	1.02	0.78, 1.33
CPT v topical corticosteroid (potent) + CPT	8	1	174/176	-0.22	0.12	-1.83	/	0.80	0.63, 1.02
CPT (twice daily) v CPT (once daily)	8	1	174/174	0.41	0.16	2.59	/	1.51	1.11, 2.07
CPT v coal tar	6	1	30/30	1.70	0.72	2.35	/	5.5	1.33, 22.73
CPT v "short-contact" dithranol	8	1	239/239	0.39	0.07	5.31	/	1.47	1.28, 1.70
	12	1	161/144	0.25	0.11	2.16	/	1.28	1.02, 1.60
CPT v tacalcitol	8	1	145/142	0.32	0.12	2.61	/	1.38	1.08, 1.75
CPT v UVB phototherapy + CPT	6	1	101/101	-0.15	0.11	-1.46	/	0.86	0.70, 1.05
	8	1	101/101	-0.12	0.14	-0.84	/	0.89	0.68, 1.17

lnRR : log to the base e of the rate ratio; SE : standard error; z : standard normal statistic; χ^2_{heter} : chi-squared test for heterogeneity; RR : rate ratio; 95%CI : 95% confidence interval.

Figure 4.3 : Investigator overall assessment: mean (95% confidence interval) rate ratios for *marked improvement or clearance* between treatments.

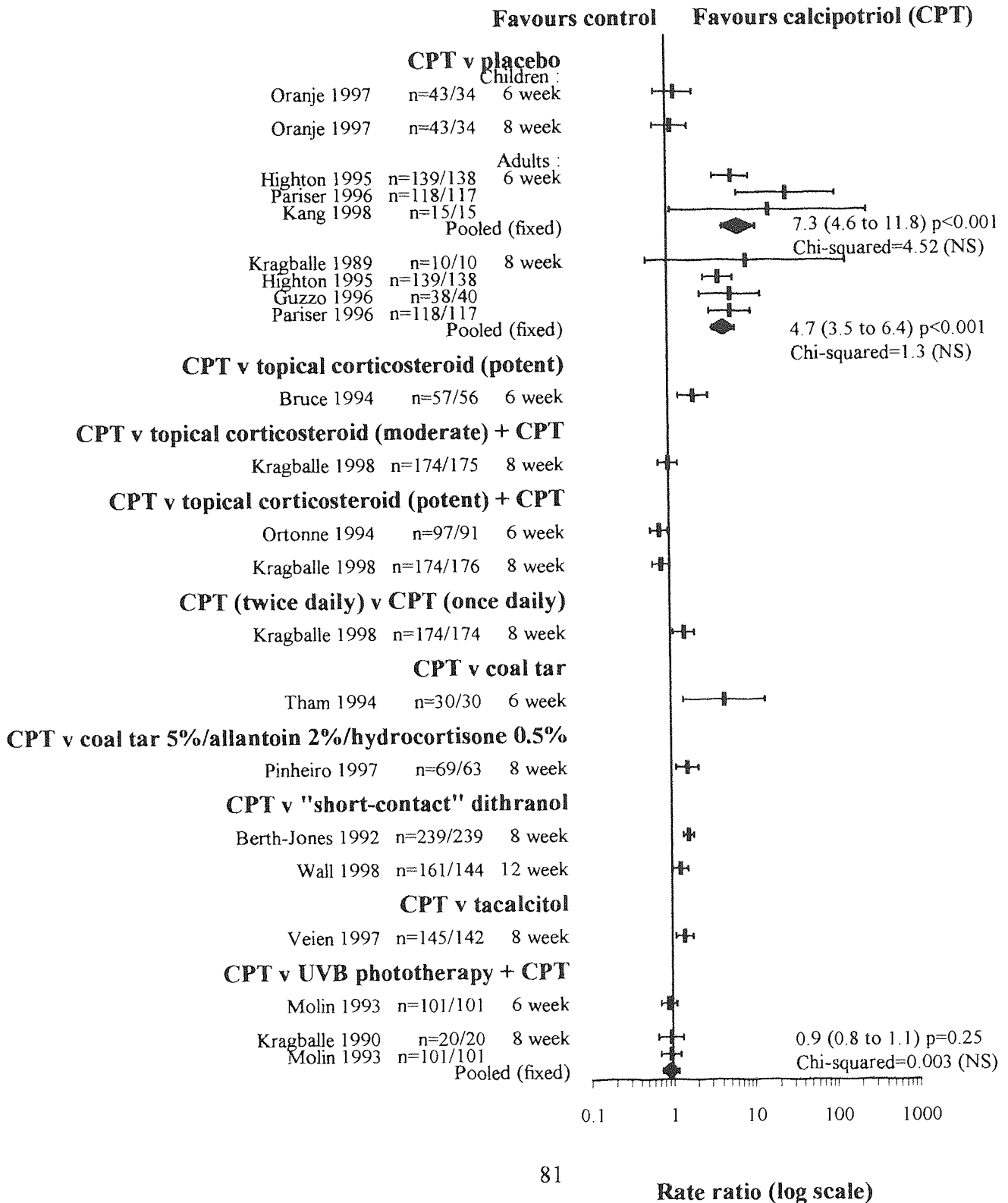


Table 4.4 : Investigator overall assessment : Antipsoriatic efficacy (response rate ratio RR) for marked improvement or better between treatments.

Comparison	Treatment duration (weeks)	No. of trials	No. of patients (CPT / control)	Response RR					
				InRR	SE	Z	χ^2_{heter}	RR	95% CI
CPT v placebo (children)	6	1	43/34	0.20	0.27	0.72	/	1.22	0.71, 2.08
	8	1	43/34	0.10	0.25	0.41	/	1.11	0.68, 1.80
CPT v placebo (adults)	6	3	272/270	2.00	0.24	8.23	4.52	7.36	4.58, 11.84
	8	4	305/305	1.55	0.16	9.88	1.31	4.70	3.46, 6.39
CPT v topical corticosteroid (potent)	6	1	57/56	0.68	0.22	3.09	/	1.96	1.28, 3.02
CPT v topical corticosteroid (moderate) + CPT	8	1	174/175	-0.04	0.13	-0.28	/	0.96	0.74, 1.25
CPT v topical corticosteroid (potent) + CPT	6	1	97/91	-0.29	0.12	-2.46	/	0.75	0.59, 0.94
	8	1	174/176	-0.25	0.12	-2.04	/	0.78	0.62, 0.99
CPT (twice daily) v CPT (once daily)	8	1	174/174	0.35	0.16	2.25	/	1.42	1.05, 1.92
CPT v coal tar	6	1	30/30	1.47	0.59	2.50	/	4.33	1.37, 13.67
CPT v coal tar 5%/ allantoin 2%/ hydrocortisone 0.5%	8	1	69/63	0.43	0.16	2.62	/	1.53	1.11, 2.11
CPT v "short-contact" dithranol	8	1	239/239	0.45	0.08	5.93	/	1.57	1.35, 1.83
	12	1	161/144	0.21	0.11	1.83	/	1.23	0.99, 1.53
CPT v tacalcitol	8	1	145/142	0.33	0.12	2.61	/	1.38	1.08, 1.77
CPT v UVB phototherapy + CPT	6	1	101/101	-0.12	0.11	-1.17	/	0.88	0.72, 1.09
	8	2	121/121	-0.07	0.11	-0.68	0.002	0.93	0.76, 1.15

Placebo - A total of 1185 patients participated in 8 calcipotriol versus placebo trials. At 6 and 8 weeks, the results from the meta-analysis indicate that in adults calcipotriol was more effective than placebo. The rate ratio at 8 weeks was 2.9 (95% confidence interval 1.7 to 5.0) in the patients' overall assessment of response and 4.7 (3.5 to 6.4) in the investigators' overall assessment. The mean difference in the percentage change in PASI at 8 weeks was 44.1% (27.8% to 60.4%). In children, based on the results of one trial (Oranje *et al.* 1997), there was no significant difference between the treatments using all three measures of efficacy.

Topical corticosteroids - Comparison of the effects estimated from the calcipotriol versus potent topical corticosteroid trials showed that at 6 weeks calcipotriol was significantly more effective than potent topical corticosteroid agents on the basis of all three response measures. The pooled mean difference in the percentage change in PASI was 6.5% (2.4% to 10.6%) with a fixed effect model (Figure 4.1). At 8 weeks, however, on the basis of two trials there was no statistically significant difference. Compared against very potent topical corticosteroids, there was also no statistically significant difference between the two treatments; the pooled mean difference in the percentage change in PASI was 10.2% (-0.7% to 21.1%). A combination regimen of a potent topical corticosteroid plus calcipotriol, however, proved more effective than calcipotriol monotherapy. At 6 and 8 weeks, the mean differences in percentage change in PASI were -8% (-15.6% to -0.4%) and -6.6% (-13.1% to -0.2%), respectively. The corresponding rate ratio for marked

improvement or cleared at 8 weeks in the patients' overall assessment was 0.8 (0.6 to 1.0).

Calcipotriol (once daily) - Two trials compared twice-daily and once-daily regimens in a total of 480 patients (Baiocchi *et al.* 1997, Kragballe *et al.* 1998). Efficacy based on the percentage change in PASI showed superiority for the twice-daily regimen; the pooled mean difference in effect was 5.5% (1.2% to 9.8%).

Calcitriol - Calcipotriol had a greater effect over twice-daily topical calcitriol (Figure 4.1). One parallel trial (Bourke *et al.* 1997a) found that at 6 and 8 weeks, the mean difference in percentage change in PASI was 34.2% (9.8% to 58.7%) and 50.9% (30.6% to 71.2%), respectively.

Coal tar - One trial (Tham *et al.* 1994) showed that at 6 weeks topical calcipotriol was superior to coal tar. The mean difference in percentage change in PASI was 38.9% (26.9% to 50.9%). The results were consistent with those obtained using the patients' and the investigators' overall assessments of at least marked improvement; the corresponding rate ratios were 5.5 (1.3 to 22.7) and 4.3 (1.4 to 13.7).

Coal tar 5%/ allantoin 2%/ hydrocortisone 0.5% - Using the investigators' overall assessment, the rate ratio for marked improvement or cleared in a trial of 122 patients was 1.5 (1.1 to 2.1), indicating that calcipotriol was

significantly better than coal tar 5%/ allantoin 2%/ hydrocortisone 0.5% (Figure 4.3).

“Short-contact” dithranol - Overall, calcipotriol was significantly more effective than “short-contact” dithranol on the basis of all three response measures. At 8 weeks, the mean difference in percentage change in PASI was 15.4% (10.1% to 20.7%). At 8 and 12 weeks, the rate ratios for marked improvement or cleared in the patients’ overall assessment were 1.5 (1.3 to 1.7) and 1.3 (1.0 to 1.6). Similar results were obtained with the investigators’ overall assessment; the corresponding rate ratios at 8 and 12 weeks were 1.6 (1.4 to 1.8) and 1.2 (1.0 to 1.5).

Tacalcitol - Only one trial of 287 patients compared once-daily treatment with tacalcitol with twice-daily treatment with calcipotriol (Veien *et al.* 1997). Using the patients’ and investigators’ overall assessments of marked improvement or better, calcipotriol proved significantly more effective than tacalcitol after 8 weeks of treatment; both rate ratios were equal at 1.4 (1.1 to 1.8).

UVB phototherapy and calcipotriol - The point estimates suggest efficacy in favour of the UVB phototherapy and calcipotriol combinations versus calcipotriol monotherapy, but there was no statistical difference between the treatments with the exception of the PASI as the measure of outcome (Figure 4.1). At 6 and 8 weeks, the mean differences in percentage change in PASI

were -8% (-14.9% to -1.1%) and -14.2% (-27.0% to -1.5%), respectively.

4.3.3 Withdrawal from treatment

Comparison of withdrawal rates showed that significantly more patients were withdrawn from placebo treatment compared with calcipotriol (Table 4.5). Surprisingly, more patients were withdrawn from treatment with very potent topical corticosteroids. Further examination of these trial results, however, revealed that the majority of patients (32/48) dropped-out as a result of resolution of their psoriasis before trial completion. In contrast, “short-contact” dithranol resulted in a significantly higher overall withdrawal rate but also a higher withdrawal rate due to adverse effects of treatment. On average, treating 23 patients with “short-contact” dithranol will lead to one more patient dropping-out of treatment due to adverse effects than if they were treated with calcipotriol.

Table 4.5 : Comparison of withdrawal rates and risk of adverse effects (95% confidence intervals).

Comparison	Withdrawal (total)	Withdrawal (adverse effects)	Lesional/perilesional irritation	Facial / scalp irritation	Exacerbation
Calcipotriol v placebo					
Crude rate	30/396 v 42/314	11/461 v 13/379	60/433 v 45/349	22/294 v 0/211	10/471 v 16/389
Weighted RR	0.53 (0.34 to 0.84)*	0.73 (0.34 to 1.58)	1.00 (0.69 to 1.44)	4.39 (1.05 to 18.42)*	0.57 (0.27 to 1.21)
Weighted RD	-0.05 (-0.10 to -0.01)*	-0.01 (-0.03 to 0.02)	0.02 (-0.03 to 0.06)	0.05 (-0.01 to 0.11)	-0.01 (-0.04 to 0.01)
Calcipotriol v topical corticosteroid (potent)					
Crude rate	49/514 v 36/514	13/817 v 8/816	110/859 v 41/859	25/415 v 1/415	18/859 v 24/859
Weighted RR	1.33 (0.88 to 1.99)	1.63 (0.68 to 3.91)	2.49 (1.76 to 3.53)*	16.05 (3.09 to 83.36)*	0.74 (0.39 to 1.40)
Weighted RD	0.03 (0.00 to 0.06)	0.00 (0 to 0.01)	0.10 (0.03 to 0.17)*†	0.06 (-0.02 to 0.13)	0.00 (-0.01 to 0.01)
Calcipotriol v topical corticosteroid (very potent)					
Crude rate	20/80 v 48/80	3/80 v 2/80	3/80 v 1/80	0/80 v 2/80	0/80 v 0/80
Weighted RR	0.42 (0.28-0.63)*	1.40 (0.28 to 6.91)	2.28 (0.33 to 15.80)	0.33 (0.04 to 3.12)	1 (0.06 to 15.63)
Weighted RD	-0.34 (-0.47 to -0.20)*	0.01 (-0.05 to 0.07)	0.02 (-0.03 to 0.08)	-0.02 (-0.06 to 0.02)	0 (-0.03 to 0.03)
Calcipotriol v topical corticosteroid (moderate) plus calcipotriol					
Crude rate	17/174 v 12/175	6/174 v 3/175	55/174 v 28/175	17/174 v 9/175	NR
RR	1.42 (0.70 to 2.89)	2.01 (0.51 to 7.92)	1.98 (1.32 to 2.96)*	1.90 (0.87 to 4.15)	NR
RD	0.03 (-0.03 to 0.09)	0.02 (-0.02 to 0.05)	0.16 (0.07 to 0.24)*‡	0.05 (-0.01 to 0.10)	NR
Calcipotriol v topical corticosteroid (potent) plus calcipotriol					
Crude rate	30/400 v 20/391	14/358 v 6/349	86/313 v 30/309	17/174 v 5/176	1/139 v 0/133
Weighted RR	1.43 (0.82 to 2.48)	2.25 (0.87 to 5.82)	2.70 (1.84 to 3.96)*	3.44 (1.30 to 9.12)*	1.86 (0.16 to 21.93)
Weighted RD	0.03 (-0.01 to 0.06)	0.02 (0.00 to 0.04)	0.18 (0.12 to 0.24)*‡ ¹	0.07 (0.02 to 0.12)*‡ ²	0.01 (-0.02 to 0.03)
Calcipotriol v betamethasone dipropionate + 3% salicylic acid					
Crude rate	20/80 v 17/80	6/80 v 2/80	8/80 v 0/80	NR	NR
RR	1.18 (0.67 to 2.08)	3 (0.62 to 14.42)	17 (0.10 to 289.67)*	NR	NR
RD	0.04 (-0.09 to 0.17)	0.05 (-0.02 to 0.12)	0.10 (0.03 to 0.17)*‡ ³	NR	NR

Table 4.5 (cont.) : Comparison of withdrawal rates and risk of adverse effects (95% confidence intervals).

Comparison	Withdrawal (total)	Withdrawal (adverse effects)	Lesional/perilesional irritation	Facial / scalp irritation	Exacerbation
Calcipotriol (twice daily) v calcipotriol (once daily)					
Crude rate	32/306 v 30/306	13/306 v 14/306	72/306 v 53/306	17/174 v 8/174	3/132 v 3/132
Weighted RR	1.06 (0.66 to 1.71)	0.93 (0.44 to 1.95)	1.35 (0.99 to 1.84)	2.13 (0.94 to 4.79)	1 (0.21 to 4.86)
Weighted RD	0.01 (-0.04 to 0.05)	0.00 (-0.04 to 0.03)	0.06 (0.00 to 0.11)	0.05 (0.00 to 0.11)	0 (-0.04 to 0.04)
Calcipotriol v calcitriol					
Crude rate	4/12 v 4/12	0/12 v 0/12	NR	NR	NR
RR	1 (0.32 to 3.1)	1 (0.02 to 46.71)	NR	NR	NR
RD	0 (-0.38 to 0.38)	0 (-0.15 to 0.15)	NR	NR	NR
Calcipotriol v coal tar 5%/ allantoin 2%/ hydrocortisone 0.5%					
Crude rate	4/69 v 6/63	1/69 v 3/63	13/69 v 7/63	NR	1/69 v 1/63
RR	0.61 (0.18 to 2.06)	0.30 (0.03 to 2.85)	1.70 (0.72 to 3.98)	NR	0.91 (0.06 to 14.29)
RD	-0.04 (-0.13 to 0.05)	-0.03 (-0.09 to 0.03)	0.08 (-0.04 to 0.20)	NR	0.00 (-0.04 to 0.04)
Calcipotriol v coal tar					
Crude rate	0/15 v 0/15	1/45 v 0/45	3/45 v 0/45	0/45 v 0/45	1/45 v 1/45
RR	1 (0.02 to 47.38)	1.93 (0.17 to 22.26)	3.44 (0.34 to 35.37)	1 (0.06 to 15.47)	0.99 (0.11 to 9.11)
RD	0 (-0.12 to 0.12)	0.02 (-0.05 to 0.09)	0.05 (-0.04 to 0.13)	0 (-0.06 to 0.06)	0.01 (-0.07 to 0.09)
Calcipotriol v "short contact" dithranol					
Crude rate	65/489 v 104/465	15/489 v 38/465	61/353 v 149/346	10/239 v 1/239	3/239 v 3/239
Weighted RR	0.59 (0.45 to 0.76)*	0.37 (0.21 to 0.66)*	0.43 (0.33 to 0.55)*	10 (1.29 to 77.51)*	1 (0.20 to 4.91)
Weighted RD	-0.07 (-0.12 to -0.03)*	-0.04 (-0.07 to -0.02)*	-0.26 (-0.40 to -0.13)*‡ ⁴	0.04 (0.01 to 0.06)*‡ ³	0 (-0.02 to 0.02)
Calcipotriol v tacalcitol					
Crude rate	5/145 v 4/142	5/145 v 4/142	NR	NR	NR
RR	1.22 (0.34 to 4.47)	1.22 (0.34 to 4.47)	NR	NR	NR
RD	0.01 (-0.03 to 0.05)	0.01 (-0.03 to 0.05)	NR	NR	NR
Calcipotriol v UVB phototherapy plus calcipotriol					
Crude rate	NR	NR	14/101 v 16/101	3/121 v 3/121	2/101 v 2/101
Weighted RR	NR	NR	0.88 (0.45 to 1.70)	1 (0.21 to 4.67)	1 (0.14 to 6.96)
Weighted RD	NR	NR	-0.02 (-0.12 to 0.08)	0 (-0.03 to 0.03)	0 (-0.04 to 0.04)

* p≤0.05 for difference in rates. NR: not reported

†NNT was 10 (6 to 34); ‡NNT was 7 (4 to 15); †¹NNT was 6 (4 to 8); ‡²NNT was 15 (9 to 54); ‡³NNT was 11 (6 to 34); ‡⁴NNT was -4 (-8 to -3); ‡⁵NNT was 27 (15 to 91).

4.3.4 Adverse effects

Overall, the most common adverse effects were lesional/perilesional irritation, facial/scalp irritation, or exacerbation of psoriasis. Table 4.5 summarises the data on adverse effects expressed as the rate ratio (relative risk, RR) and the rate difference (risk difference, RD). Compared against potent topical corticosteroids, calcipotriol caused significantly more skin irritation. On average, for every 10 patients treated with calcipotriol, one more patient experienced lesional/perilesional irritation than if they were treated with a potent topical corticosteroid. Similarly, calcipotriol monotherapy caused significantly more irritation than a combination regimen of calcipotriol plus a moderate or potent topical corticosteroid. When compared against calcipotriol plus a potent corticosteroid, a mean number needed to treat of 6 was calculated. This means that for every 6 patients treated calcipotriol alone, one more patient experienced lesional/perilesional irritation than if they were treated with the combination regimen.

In contrast, "short-contact" dithranol was significantly more irritant than calcipotriol. On average, treating 4 patients with dithranol will lead to one more patient experiencing lesional/perilesional irritation than if they were receiving calcipotriol. Facial/scalp irritation, however, occurred less frequently with dithranol compared to calcipotriol. For every 27 patients treated with calcipotriol, one more patient experienced facial irritation than if they were treated with dithranol.

4.3.5 Sensitivity analysis

Given that many of the trials included in the meta-analysis only reported on the patients remaining at each assessment point, the sensitivity analysis compared the intention-to-treat results for efficacy with those obtained if only the remaining patients were considered. Irrespective of the method, there were no significant differences in effect between the two analyses. With the placebo-controlled trials, the following points were also examined: (i) including 1 trial in which only children were treated (Oranje *et al.* 1997), and (ii) excluding 1 trial in which a once-daily regimen of calcipotriol was used (Pariser *et al.* 1996). In pooling all placebo-controlled studies, there was only a significant difference in efficacy on the basis of the investigators' overall assessment of response (Table 4.6). There was also no difference in effect, using the investigators' overall assessment, when the once-daily calcipotriol trial was excluded (3.1; 1.2 to 8.0) when compared with the overall pooled estimate of effect (3.6; 1.7 to 7.6).

Table 4.6 : Sensitivity analysis (95% confidence interval) with respect to type of patient treated in placebo-controlled trials at 8 weeks.

Patients treated	Mean difference in PASI%	Rate ratio for POA	Rate ratio for IOA
Adults	44.1% (27.8% to 60.4%)	2.9 (1.7 to 5.0)	4.7 (3.5 to 6.4)
Children	10.6% (-10.1% to 31.3%)	0.8 (0.5 to 1.4)	1.1 (0.7 to 1.8)
Overall	28.0% (-4.8% to 60.8%)	1.6 (0.5 to 5.3)	3.6 (1.7 to 7.6)

POA: patients' overall assessment of marked improvement or better; IOA: investigators' overall assessment of marked improvement or better.

4.4 Discussion

The systematic review has confirmed that calcipotriol is effective in the treatment of mild-to-moderate chronic plaque psoriasis. Overall, calcipotriol was superior to calcitriol, coal tar, coal tar 5%/allantoin 2%/hydrocortisone 0.5%, “short-contact” dithranol, and tacalcitol. Comparable effects were seen using potent topical corticosteroids after 8 weeks of treatment.

4.4.1 Implications of the results

Several clinical implications emerge from the analysis. Although twice-daily application of calcipotriol was statistically superior to once-daily dosing, the results of the meta-analysis suggest that once-daily application may be sufficient for many patients. In particular, it has been demonstrated that once-daily application of calcipotriol is significantly more effective than placebo (Pariser *et al.* 1996). However, we found no significant difference in the incidence of skin irritation with the once-daily regimen.

The limited evidence available suggests that in the short-term management of chronic plaque psoriasis, once-daily treatment with calcipotriol and a potent topical corticosteroid is more effective and better tolerated than twice-daily treatment with calcipotriol. One possible explanation might be that corticosteroids suppress the occurrence of calcipotriol-induced irritation.

However, it is important to remember that, with long-term use topical corticosteroids have the potential to cause side-effects such as atrophy, striae, telangiectasia and masking of local infections. Systemic effects cannot also be completely ignored.

Although lesional/perilesional irritation is common, it is generally tolerated by patients and rarely requires calcipotriol withdrawal. In contrast, short-contact dithranol caused significantly more skin irritation. Importantly, this contributed to a statistically higher withdrawal rate from dithranol than with calcipotriol. There was insufficient data to determine whether the newer dithranol formulations are any less irritant than the more established products.

4.4.2 Limitations of the study

Not all the trials reported on the outcomes of interest. Therefore, to obtain the pooled estimates the trials included in the different analyses do not necessarily match. Only one trial (Wall *et al.* 1998) included quality of life (QoL) assessments and as a result QoL was not examined as an outcome in the analysis. In particular, European investigators' favoured a modified PASI as the primary measure of efficacy while trials conducted in the US tended to use an investigators' overall assessment of improvement.

Publication bias is a potential threat to the validity of any systematic review. Strenuous efforts were made to locate any unpublished studies, but the results

of a single clinical trial were relied on for some of the comparisons. Several trials were excluded from the analysis because they did not meet the inclusion criteria or failed to report on essential patient data. However, similar qualitative results were obtained in these trials which provided some confidence on the robustness of the conclusions.

A random effects model was used for some of the analysis because of heterogeneity. Potential sources of variation may include the formulation (for example, cream, ointment), the choice of topical corticosteroid, and the patient population (children/adults). Unfortunately, there were no direct head-to-head comparisons of the cream and ointment formulations, and indirect comparisons were not possible because of the sparsity of studies using calcipotriol cream at the various assessment points. Surprisingly, however, calcipotriol appeared more effective in adults than children, an observation which clearly needs further confirmation.

Since psoriasis is a chronic relapsing/remitting disease in the majority of sufferers, future trials should examine efficacy over a much longer period than 6 to 8 weeks (for example, up to 6 months), in order to capture the duration of remission following clearance of lesions which may be important to sufferers. All adverse effects may not be detected during the short duration of a randomised controlled trial, but they may emerge over time. For any chronic condition, the potential long-term risks attributable to the various treatment options should be considered.

4.5 Conclusions

The selection of topical treatments for chronic plaque psoriasis should be more rationalised by using the results of the systematic review. Pooled data from RCTs show that calcipotriol is an effective and well-tolerated treatment for mild-to-moderate chronic plaque psoriasis. Although skin irritation is relatively common, this rarely requires withdrawal of calcipotriol treatment. Potent topical corticosteroids have also emerged as equally effective agents when assessed at 8 weeks, with less short-term side-effects than calcipotriol. Future trials should focus on examining the risk-to-benefit ratios from combined regimens of calcipotriol with other topical antipsoriatic agents and include information on quality of life and disease remission.

CHAPTER 5

Systematic review of combination regimens of topical calcipotriol with systemic therapies

5.1 Introduction

It has been estimated that 23% of patients with psoriasis have disease where topical therapy is either impractical or not sufficiently effective (Liem *et al.* 1992). If these patients fail to respond to topical therapy, they are treated with phototherapy, photochemotherapy or systemic treatments. Unfortunately, the usefulness of these treatment modalities is often restricted by their toxicity. The dose-dependent nature of many of the side-effects has led to the development of combined treatment with topical therapies in an attempt to reduce the total dose of the systemic agent and thereby lessen the risk of serious side-effects. The use of combined regimens also raises a number of important questions: Are there any improvements in efficacy? Do patients experience a longer duration in remission following treatment? Are there any reductions in the overall therapy costs (economic issues)?

The concurrent use of calcipotriol with systemic agents is commonplace in many dermatology departments. Results from a survey of dermatologists using such regimens suggested that it is possible to improve efficacy over

systemic monotherapy (Katz 1997). In order to clarify these issues in a more objective manner, this chapter provides a systematic review of randomised controlled trials. The objectives were to investigate the efficacy and tolerability of combining calcipotriol with phototherapy or systemic agents in the treatment of chronic plaque psoriasis.

5.2 Methods

5.2.1 Inclusion and exclusion criteria

The following selection criteria were used to identify studies for the analysis:

Types of study - Only RCTs were included. Quality scoring was restricted to this threshold criterion because of broad support for the clinical importance of these items but less so on other items often included in quality scores.

Types of participants - Patients with chronic plaque psoriasis were eligible for inclusion. Exclusion criteria included guttate, pustular, or erythrodermic psoriasis.

Types of intervention - Calcipotriol 0.005% cream or ointment used in combination with either phototherapy or systemic antipsoriatic therapies.

Types of outcome measures

Assessment of efficacy - The efficacy criteria were :

- 1 the proportion of patients showing marked improvement or cleared in the patients' and/or investigators' overall assessments of response;
- 2 the proportion of patients cleared in the patients' and/or investigators' overall assessments of response;
- 3 the mean percentage change from baseline in PASI scores.

Assessment of tolerability - The proportion of patients experiencing cutaneous side-effects, non-cutaneous side-effects, any adverse effect, and the number of withdrawals due to adverse effects were examined.

5.2.2 Search strategy for identification of studies

Reports of RCTs were identified by computerised searches (from 1987) of the Cochrane Controlled Trials Register, Embase, Medline, and BIDS Index to Scientific and Technical Proceedings. Textwords applied to the search included calcipotriol, MC903, calcipotriene, Dovonex, Daivonex and Psorcutan. This was supplemented by searching the information database maintained by the manufacturer of calcipotriol (Leo Pharmaceuticals) and the reference lists of all retrieved RCTs. The search was most recently updated in January 1999. There were no language restrictions. Abstracts were considered; relevant information not included in the published reports was obtained by either contacting the principal author of the trial or the

manufacturer.

5.2.3 Methods of review

The methods described in Chapter 4 (see section 4.2) were used in the analysis. Dichotomous outcomes were estimated with the rate ratio (RR) and the rate difference (RD). When there were no events in one group, 0.5 was added to each cell of the 2 x 2 table. In all cases, an intention-to-treat analysis was used, whereby the denominator was taken as the number of patients randomised. The percentage change in PASI from baseline was analysed as the weighted mean difference (see section 4.2), defined as the difference between mean values in the treatment and control groups of individual trials and the mean difference weighted for trial size for groups of trials.

The method of DerSimonian & Laird (1986), as implemented by Whitehead & Whitehead (1991), was used to calculate the pooled estimates and their corresponding 95% CI. Heterogeneity between trials was examined using χ^2 tests, with $p \leq 0.05$ indicating significant heterogeneity. If there was no evidence of statistical heterogeneity, summary estimates of the effect from each trial were pooled using a fixed effects model. Otherwise, a random effects model was used. Results from fixed or random effects modelling are shown as appropriate in the tables and graphs.

5.3 Results

Thirteen reports of RCTs were identified (Appendix II), of which 11 were included in the analysis (Table 5.1). Two trials which examined the combined use of topical calcipotriol and UVB phototherapy were excluded because they reported on non-relevant outcomes for this study. Hecker & Lebwohl (1997) used the sum of the scores for erythema, plaque elevation, scaling and pruritus to arrive at a total severity score for each target site, while Dutz & Lui (1998) used a modified PASI method which was not consistent with the standard PASI scoring adopted in the remaining studies. A further five trials were excluded because of a lack of randomisation (Kokelj *et al.* 1995, Barba *et al.* 1996, Kokelj *et al.* 1997, Vázquez-López *et al.* 1997, Kokelj *et al.* 1998).

Table 5.1 : Characteristics of randomised controlled trials.

Trial	Design	Mean age (years)	Treatment duration (weeks)	Follow-up period (weeks)	Treatment		No. of patients		
					Combination	Control	Combination	Control	
Calcipotriol + UVB phototherapy v calcipotriol									
Kragballe 1990	Open-B	47	8	-	CPT bid +UVB (3 x week)	CPT bid		20	20
Molin 1993	Open-B	43.7	8	8	CPT bid + UVB (3 x week)	CPT bid		101	101
Kersher 1994	Open-B	43.5	2	-	CPT bid + UVB (5 x week)	CPT bid		20	20
Bourke 1997†	Open -P	40	4	-	CPT 100g/week + UVB (3 x week)	CPT 100g/week		10	10
Calcipotriol + UVB v placebo + UVB									
Molin 1997	DB-B	46.9	8	8	CPT bid + UVB (3 x week)	vehicle bid + UVB (3 x week)		77	77
Bourke 1997†	Open-P	40	4	-	CPT 100g/week + UVB (3 x week)	UVB (3 x week)		10	10
Ramsay 1998	SB-P	44.5	12	12	CPT bid + UVB (2 x week)	vehicle bid + UVB (3 x week)		84	80
Calcipotriol + PUVA v placebo + PUVA									
Frappez 1993	DB-P	46.2, 47	12	-	CPT bid + PUVA (3 x week)	vehicle bid + PUVA (3 x week)		54	53
Speight 1994	SB-B	50	6	6 months	CPT bid + PUVA (2 x week)	vehicle bid + PUVA (2 x week)		13	13
Aktas 1995	Open-P	36.4, 32.1	6	-	CPT bid + PUVA (4 x week)	placebo bid + PUVA (4 x week)		10	10
Calcipotriol + acitretin v placebo + acitretin									
van de Kerkhof 1998	DB-P	48.1, 47.1	12	-	CPT bid + acitretin	vehicle bid + acitretin		76	59
Calcipotriol + cyclosporin v placebo + cyclosporin									
Grossman 1994	DB-P	44.2, 43.3	6	-	CPT bid + cyclosporin	placebo bid + cyclosporin		35	34

DB-P : double-blind, parallel group; DB-B : double-blind, bilateral comparison; SB : single-blind; Open-B : open, bilateral comparison; CPT : calcipotriol (50µg/g).
† : 3-armed trial.

5.3.1 Characteristics of eligible trials

Eleven RCTs were identified which met the study's inclusion criteria. In all, this represented 756 patients randomised to treatment. Table 5.1 shows details of these trials. One trial was a three-armed parallel group study (Bourke *et al.* 1997) while the remaining 10 trials were two-armed head-to-head comparisons, 5 of which involved a bilateral (right/left) design. The duration of randomised treatment ranged from 2 to 12 weeks. All trials were randomised and controlled. Five trials were open; 2 were single-blind; and 4 were double-blind. One trial did not report on the variance of the percentage change in PASI from baseline, necessitating variance imputation (Kersher *et al.* 1994).

5.3.2 Efficacy

The results from the efficacy analyses are shown in Figures 5.1 to 5.5 and described in Tables 5.2 to 5.6.

Calcipotriol and UVB phototherapy - A combination of calcipotriol and UVB phototherapy proved more effective than calcipotriol monotherapy on the basis of the proportion of patients cleared and the mean difference in the percentage change in PASI (Figures 5.3 to 5.5). The RR for clearance at 8 weeks were 2.1 (95% confidence interval 1.2 to 3.7) in the patients' overall

assessment of response and 2.3 (1.6 to 3.4) in the investigators' overall assessment. When the proportion of patients showing marked improvement or cleared lesions were compared, there were no significant differences between the combined regimen and calcipotriol alone. The RR at 8 weeks were 1.1 (0.9 to 1.2) in the patients' assessment and 1.1 (1.0 to 1.2) in the investigators' assessment.

Likewise, when compared against UVB monotherapy in one trial of 77 patients, there was no significant difference in response with a combined regimen of calcipotriol and UVB (3 times weekly). The RR for marked improvement or better at 8 weeks were 1.0 (0.8 to 1.1) in both the patients' and the investigators' overall assessments of response, whilst the corresponding RR for clearance were 1.1 (0.7 to 1.8) and 1.0 (0.6 to 1.7), respectively. At the end of treatment (8 weeks), the mean difference in the percentage change in PASI was -1.9% (-9.2% to 5.4%).

One trial of 164 patients compared calcipotriol and UVB (2 times weekly) against placebo cream and UVB (3 times weekly) (Ramsay 1998). The efficacy results were essentially similar between the two treatment groups. There was only a significant difference in the patients' overall assessment of clearance; the RR at the end of treatment (12 weeks) was 0.6 (0.4 to 0.9). The mean difference in the percentage change in PASI was -4.1% (-14.5% to 6.3%).

Figure 5.1 : Patient overall assessment: mean (95% confidence interval)

rate ratios for *marked improvement or clearance* between treatments.

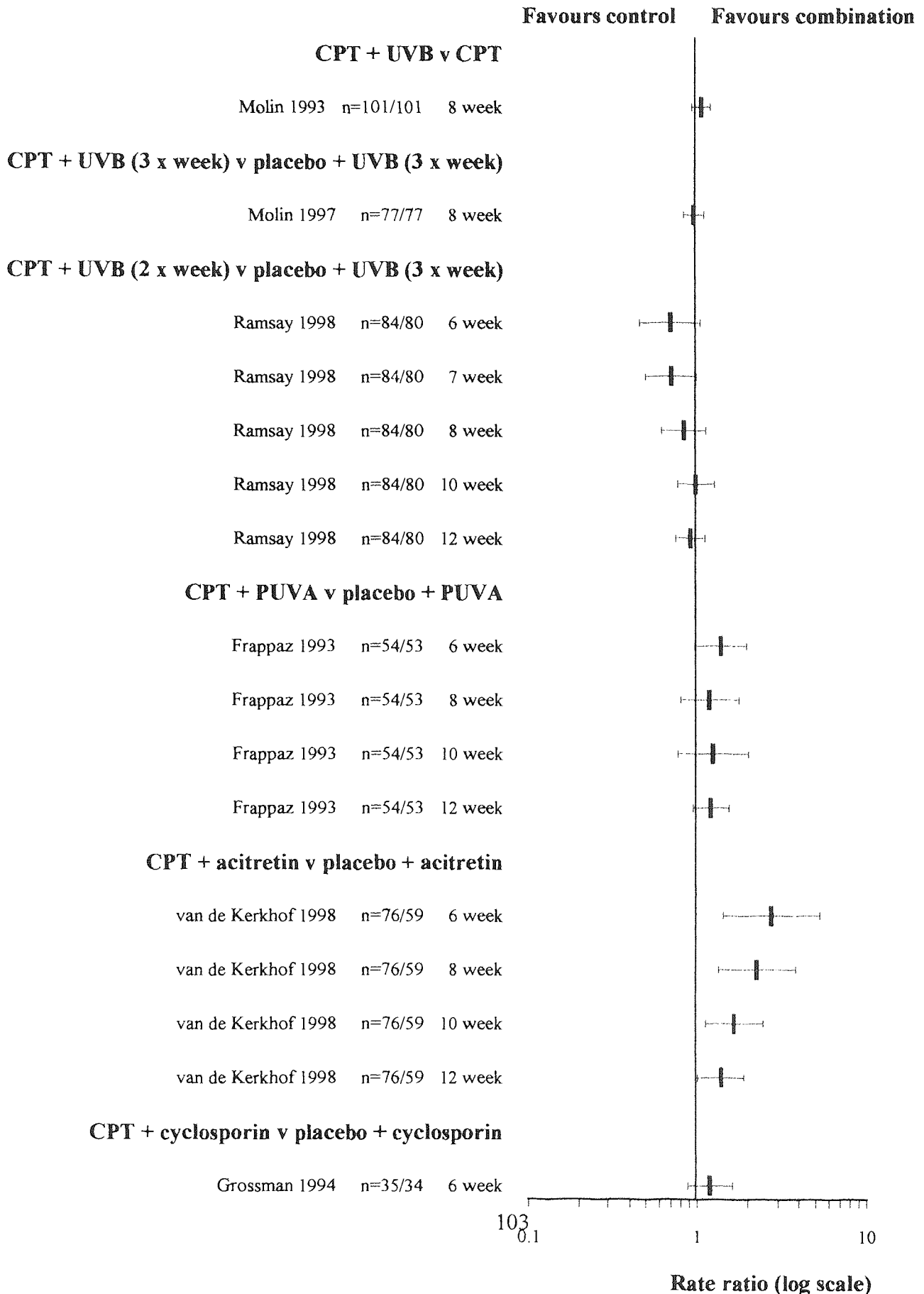


Table S.2 : Patient overall assessment : Antipsoriatic efficacy (response rate ratio RR) for marked improvement or clearance between treatments.

Comparison	Treatment duration (weeks)	No. of trials	No. of patients (CPT / control)	Response RR					
				InRR	SE	Z	χ^2_{heter}	RR	95% CI
CPT + UVB phototherapy v CPT	8	1	101/101	0.07	0.07	1.10	/	1.08	0.94, 1.22
CPT + UVB (3 x week) v placebo + UVB (3 x week)	8	1	77/77	-0.03	0.07	-0.43	/	0.97	0.84, 1.12
CPT + UVB (2 x week) v placebo + UVB (3 x week)	6	1	84/80	-0.36	0.21	-1.68	/	0.70	0.46, 1.06
	7	1	84/80	-0.34	0.17	-1.98	/	0.71	0.50, 1.00
	8	1	84/80	-0.17	0.15	-1.09	/	0.84	0.62, 1.14
	10	1	84/80	-0.01	0.13	-0.06	/	0.99	0.77, 1.28
	12	1	84/80	-0.08	0.10	-0.81	/	0.92	0.75, 1.13
CPT + PUVA v placebo + PUVA	6	1	54/53	0.33	0.18	1.80	/	1.39	0.97, 1.99
	8	1	54/53	0.18	0.20	0.87	/	1.19	0.80, 1.78
	10	1	54/53	0.23	0.25	0.91	/	1.25	0.77, 2.04
	12	1	54/53	0.19	0.13	1.53	/	1.21	0.95, 1.55
CPT + acitretin v placebo + acitretin	6	1	76/59	1.02	0.34	3.03	/	2.76	1.43, 5.32
	8	1	76/59	0.82	0.27	3.03	/	2.27	1.34, 3.86
	10	1	76/59	0.51	0.20	2.55	/	1.66	1.13, 2.46
	12	1	76/59	0.33	0.16	2.04	/	1.39	1.01, 1.90
CPT + cyclosporin v placebo + cyclosporin	6	1	35/34	0.18	0.16	1.12	/	1.19	0.88, 1.62

Figure 5.2 : Investigator overall assessment: mean (95% confidence interval) rate ratios for *marked improvement or clearance* between treatments.

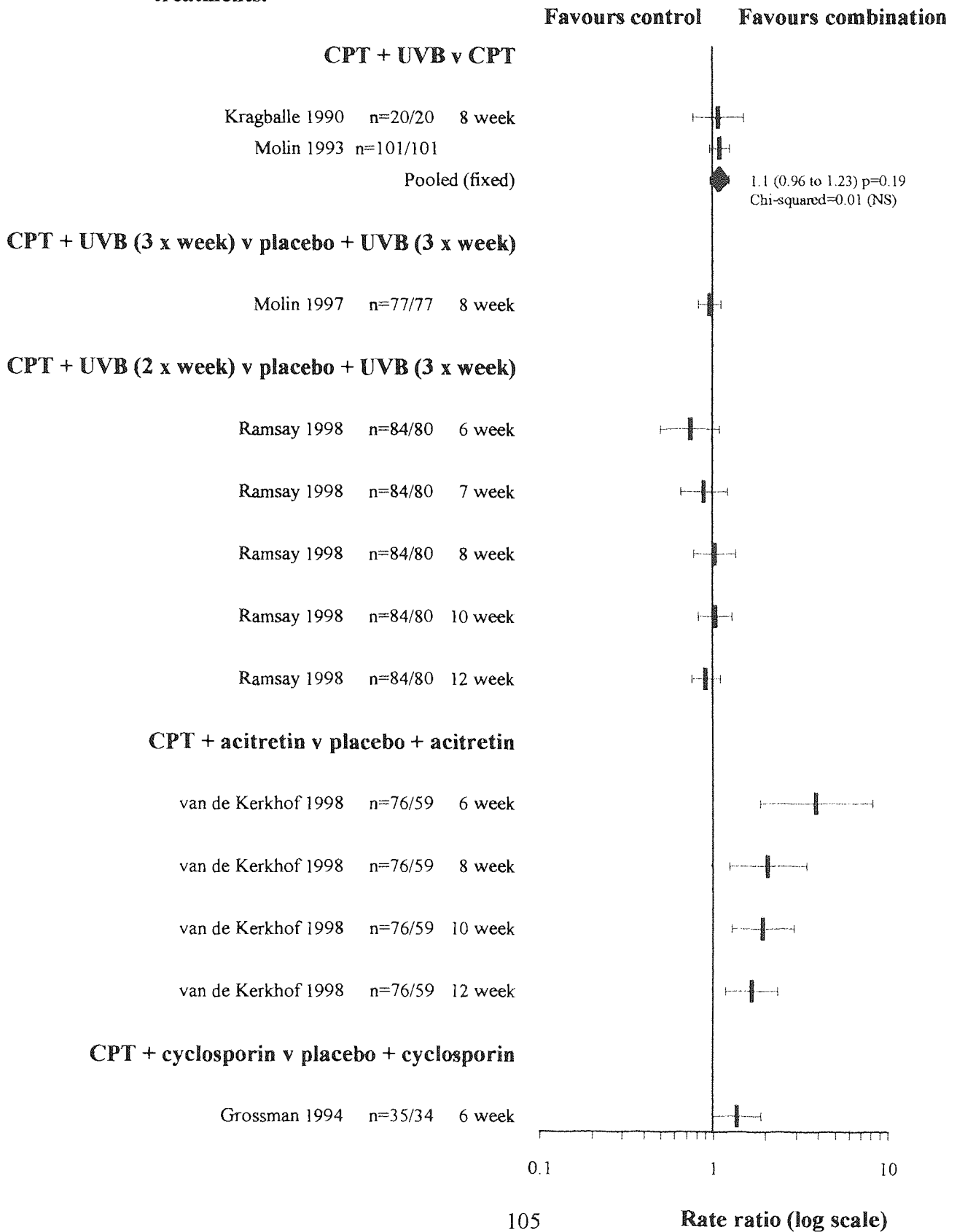


Table 5.3 : Investigator overall assessment : Antipsoriatic efficacy (response rate ratio RR) for marked improvement or clearance between treatments.

Comparison	Treatment duration (weeks)	No. of trials	No. of patients (CPT / control)	Response RR					
				lnRR	SE	Z	χ^2_{haar}	RR	95% CI
CPT + UVB phototherapy v CPT	8	2	121/121	0.08	0.06	1.32	0.01	1.09	0.96, 1.23
CPT + UVB (3 x week) v placebo + UVB (3 x week)	8	1	77/77	-0.05	0.08	-0.62	/	0.95	0.82, 1.11
CPT + UVB (2 x week) v placebo + UVB (3 x week)	6	1	84/80	-0.30	0.20	-1.52	/	0.74	0.50, 1.09
	7	1	84/80	-0.12	0.16	-0.78	/	0.88	0.65, 1.21
	8	1	84/80	0.02	0.14	0.12	/	1.02	0.77, 1.34
	10	1	84/80	0.03	0.11	0.22	/	1.03	0.82, 1.28
	12	1	84/80	-0.10	0.10	-1.01	/	0.90	0.75, 1.10
CPT + acitretin v placebo + acitretin	6	1	76/59	1.36	0.38	3.61	/	3.88	1.86, 8.11
	8	1	76/59	0.72	0.26	2.75	/	2.05	1.23, 3.42
	10	1	76/59	0.65	0.21	3.12	/	1.92	1.27, 2.89
	12	1	76/59	0.50	0.18	2.84	/	1.65	1.17, 2.33
CPT + cyclosporin v placebo + cyclosporin	6	1	35/34	0.31	0.17	1.85	/	1.36	0.98, 1.88

Figure 5.3 : Patient overall assessment: mean (95% confidence interval)

rate ratio for *cleared psoriasis* between treatment groups.

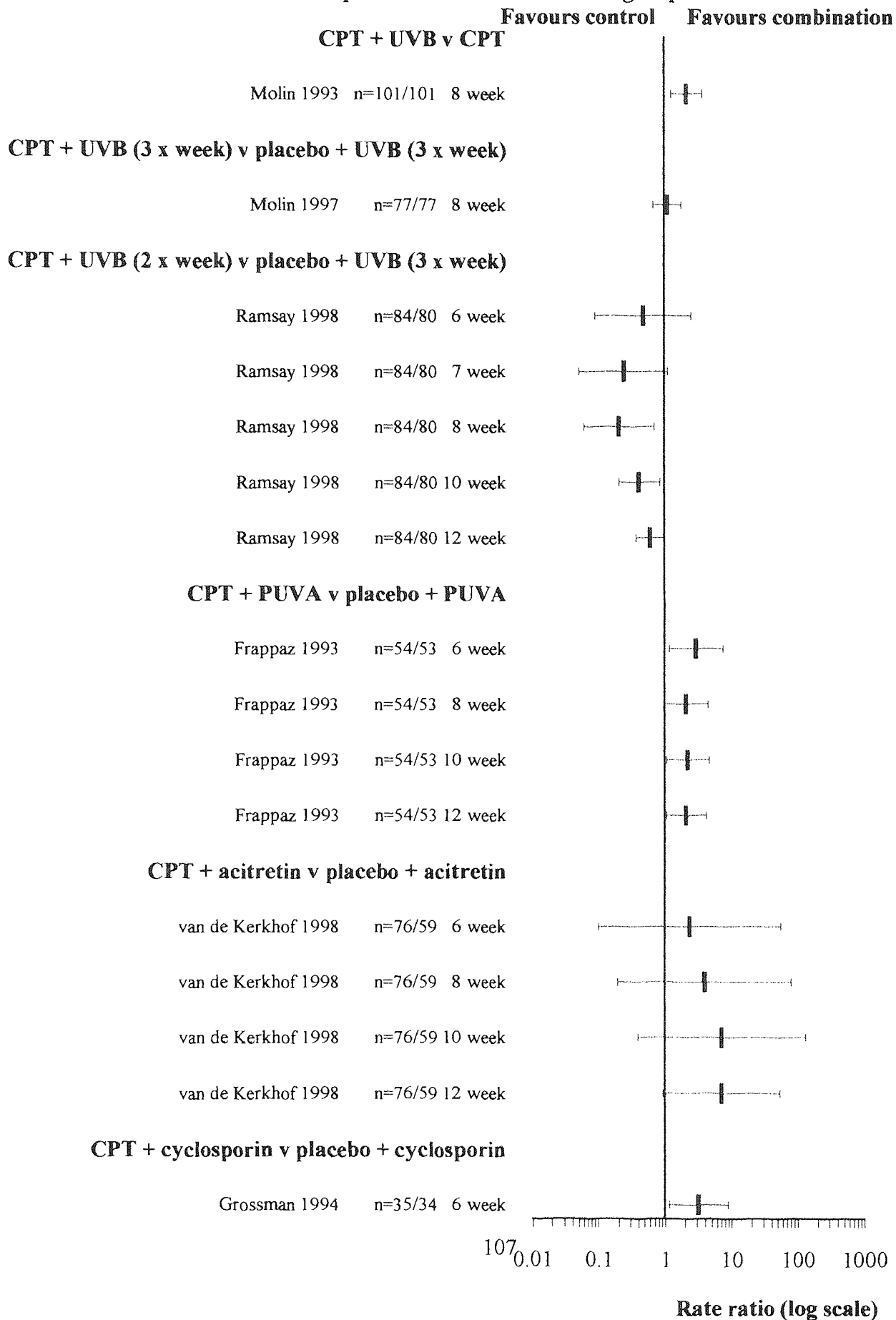


Table 5.4 : Patient overall assessment : Antipsoriatic efficacy (response rate ratio RR) for cleared psoriasis between treatments.

Comparison	Treatment duration (weeks)	No. of trials	No. of patients (CPT / control)	Response RR					
				lnRR	SE	Z	χ^2_{heter}	RR	95% CI
CPT + UVB phototherapy v CPT	8	1	101/101	0.76	0.28	2.74	/	2.13	1.24, 3.67
CPT + UVB (3 x week) v placebo + UVB (3 x week)	8	1	77/77	0.09	0.25	0.35	/	1.09	0.67, 1.77
CPT + UVB (2 x week) v placebo + UVB (3 x week)	6	1	84/80	-0.74	0.85	-0.87	/	0.48	0.09, 2.53
	7	1	84/80	-1.44	0.77	-1.85	/	0.24	0.05, 1.09
	8	1	84/80	-1.59	0.62	-2.58	/	0.20	0.06, 0.68
	10	1	84/80	-0.90	0.37	-2.44	/	0.41	0.20, 0.84
	12	1	84/80	-0.52	0.24	-2.18	/	0.60	0.37, 0.95
CPT + PUVA v placebo + PUVA	6	1	54/53	1.08	0.48	2.26	/	2.94	1.15, 7.53
	8	1	54/53	0.74	0.38	1.92	/	2.09	0.99, 4.42
	10	1	54/53	0.79	0.38	2.09	/	2.21	1.05, 4.64
	12	1	54/53	0.73	0.36	2.05	/	2.07	1.03, 4.16
CPT + acitretin v placebo + acitretin	6	1	76/59	0.85	1.62	0.52	/	2.34	0.10, 56.37
	8	1	76/59	1.36	1.54	0.88	/	3.90	0.19, 79.65
	10	1	76/59	1.95	1.48	1.32	/	7.01	0.39, 127.74
CPT + cyclosporin v placebo + cyclosporin	12	1	76/59	1.94	1.04	1.87	/	6.99	0.91, 53.62
	6	1	35/34	1.15	0.52	2.22	/	3.16	1.14, 8.72

Figure 5.4 : Investigator overall assessment: mean (95% confidence

interval) rate ratios for *cleared psoriasis* between treatment groups.

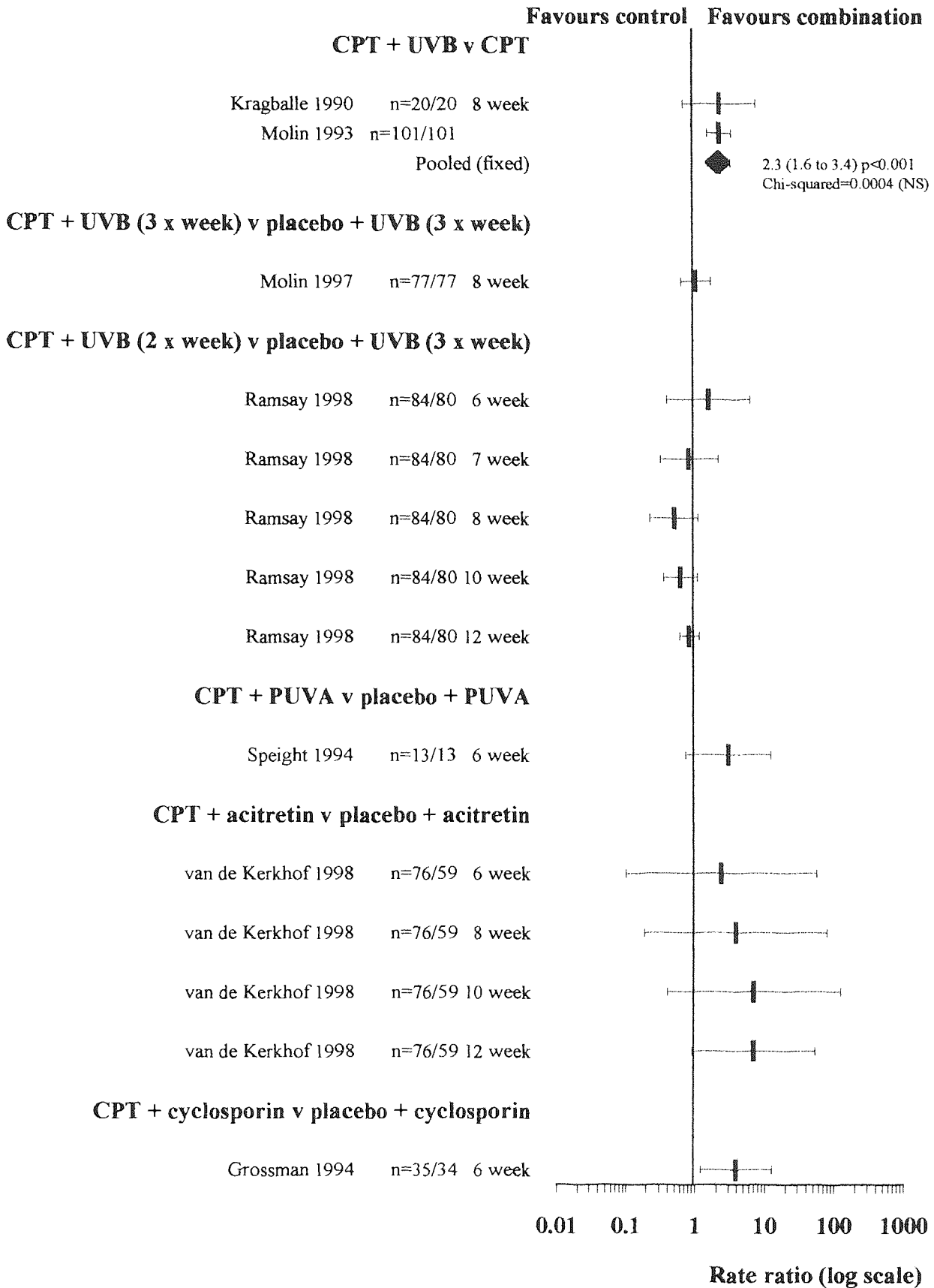


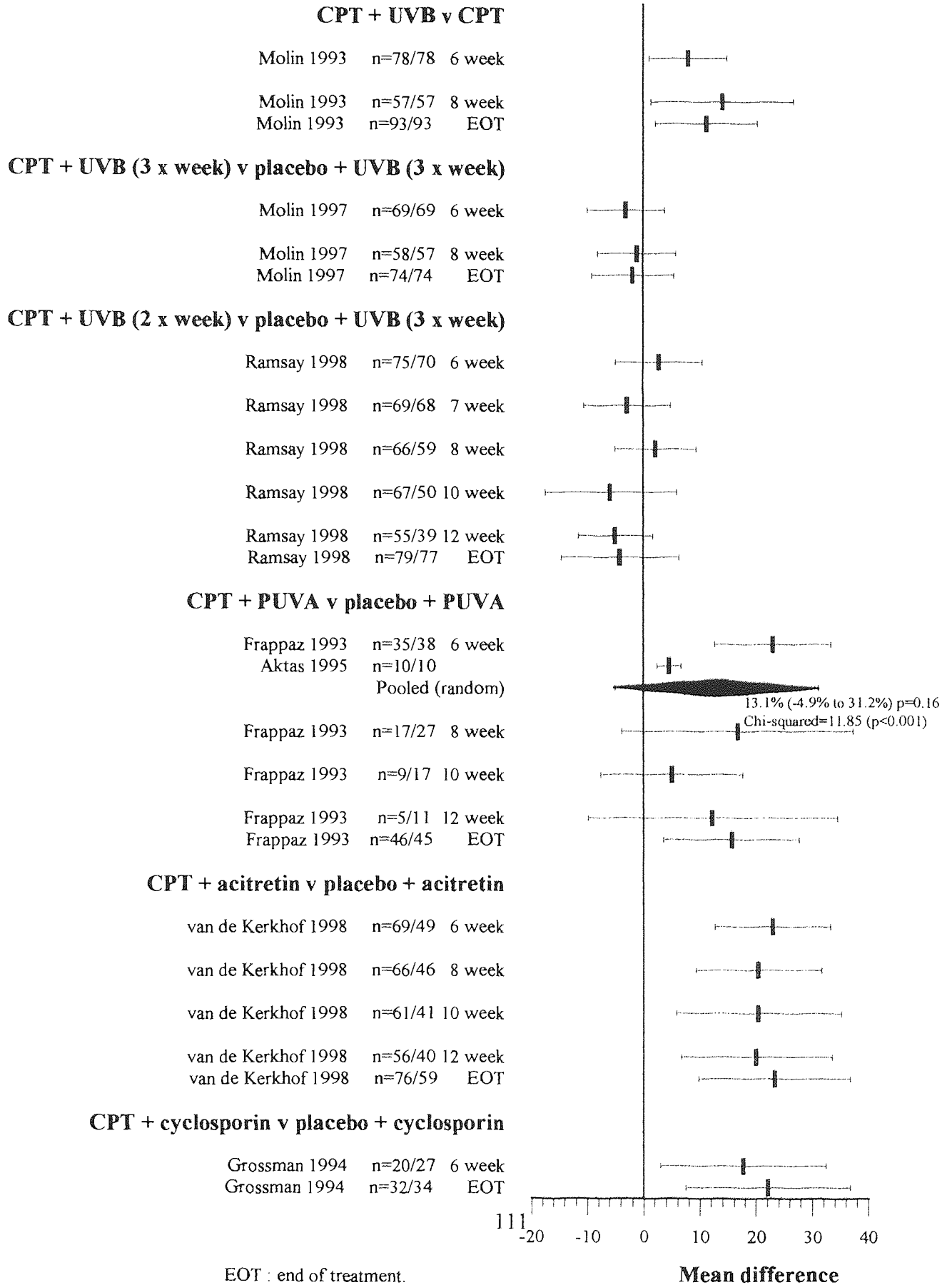
Table 5.5 : Investigator overall assessment : Antipsoriatic efficacy (response rate ratio RR) for cleared psoriasis between treatments.

Comparison	Treatment duration (weeks)	No. of trials	No. of patients (CPT / control)	Response RR					
				InRR	SE	Z	χ^2_{heter}	RR	95% CI
CPT + UVB phototherapy v CPT	8	2	121/121	0.84	0.20	4.28	0.0004	2.31	1.57, 3.38
CPT + UVB (3 x week) v placebo + UVB (3 x week)	8	1	77/77	0.04	0.25	0.18	/	1.05	0.64, 1.71
CPT + UVB (2 x week) v placebo + UVB (3 x week)	6	1	84/80	0.46	0.71	0.65	/	1.59	0.39, 6.43
	7	1	84/80	-0.18	0.49	-0.37	/	0.83	0.32, 2.19
	8	1	84/80	-0.68	0.41	-1.66	/	0.51	0.23, 1.13
	10	1	84/80	-0.48	0.29	-1.63	/	0.62	0.35, 1.10
	12	1	84/80	-0.18	0.17	-1.07	/	0.83	0.60, 1.16
CPT + PUVA v placebo + PUVA	6	1	13/13	1.10	0.72	1.53	/	3.00	0.74, 12.21
CPT + acitretin v placebo + acitretin	6	1	76/59	0.85	1.62	0.52	/	2.34	0.10, 56.37
	8	1	76/59	1.36	1.54	0.88	/	3.90	0.19, 79.65
	10	1	76/59	1.95	1.48	1.32	/	7.01	0.39, 127.74
	12	1	76/59	1.94	1.04	1.87	/	6.99	0.91, 53.62
CPT + cyclosporin v placebo + cyclosporin	6	1	35/34	1.36	0.60	2.27	/	3.89	1.20, 12.57

Figure 5.5 : Mean (95% confidence interval) differences in percentage

change in PASI from baseline between treatment groups.

Favours control Favours combination



EOT : end of treatment.

Table 5.6 : Antipsoriatic efficacy (mean difference in percentage change in PASI from baseline, PASI%) between treatments.

Comparison	Treatment duration (weeks)	No. of trials	No. of patients (combination/ control)	PASI%				
				d	SE	Z	95% CI	χ^2_{heter}
CPT + UVB phototherapy v CPT	6	1	78/78	8.00	3.54	2.26	1.06, 14.94	/
	8	1	57/57	14.20	6.51	2.18	1.45, 26.95	/
	EOT	1	93/93	11.40	4.67	2.44	2.25, 20.55	/
CPT + UVB (3 x week) v placebo + UVB (3 x week)	6	1	69/69	-3.10	3.55	-0.87	-10.06, 3.86	/
	8	1	58/57	-1.10	3.53	-0.31	-8.03, 5.83	/
	EOT	1	74/74	-1.90	3.74	-0.51	-9.24, 5.44	/
CPT + UVB (2 x week) v placebo + UVB (3 x week)	6	1	75/70	2.90	3.96	0.73	-4.87, 10.67	/
	8	1	66/59	2.30	3.67	0.63	-4.89, 9.49	/
	12	1	55/39	-4.90	3.40	-1.44	-11.57, 1.77	/
CPT + PUVA v placebo + PUVA	EOT	1	79/77	-4.10	5.33	-0.77	-14.55, 6.35	/
	6	2	45/48	13.13	9.22	1.42	-4.94, 31.21	11.85
	8	1	17/27	16.80	10.51	1.60	-3.80, 37.40	/
CPT + acitretin v placebo + acitretin	12	1	5/11	12.30	11.34	1.09	-9.92, 34.52	/
	EOT	1	46/45	15.70	6.15	2.55	3.65, 27.75	/
	6	1	69/49	23.00	5.22	4.40	12.76, 33.24	/
CPT + cyclosporin v placebo + cyclosporin	12	1	56/40	20.10	6.84	2.94	6.69, 33.51	/
	EOT	1	76/59	23.30	6.89	3.38	9.80, 36.80	/
	6	1	20/27	17.73	7.49	2.37	3.04, 32.42	/
EOT	1	32/34	22.10	7.48	2.96	7.44, 36.76	/	

Calcipotriol and PUVA phototherapy - Three trials compared calcipotriol and PUVA against placebo ointment and PUVA in a total of 140 patients (Frappaz & Thivolet 1993, Speight & Farr 1994, Aktas *et al.* 1995). There was no significant difference in the proportion of patients reporting marked improvement or cleared lesions in the patients' assessment; the RR at 12 weeks was 1.2 (0.9 to 1.6). The corresponding RR for clearance was 2.1 (1.0 to 4.2). In contrast, the PASI results show an improved response to PUVA with calcipotriol. At the end of treatment (12 weeks), the mean difference in the percentage change in PASI was 15.7% (3.6% to 27.8%).

Calcipotriol and acitretin - One trial of 135 patients compared calcipotriol and acitretin against placebo ointment and acitretin (van de Kerkhof *et al.* 1998). On the basis of the proportion of patients showing at least marked improvement and the percentage change in PASI, calcipotriol had a significant additional effect to acitretin at every assessment point during treatment. At the end of treatment (12 weeks), the RR for marked improvement or cleared lesions were 1.4 (1.0 to 1.9) in the patients' assessment and 1.6 (1.2 to 2.3) in the investigators' assessment. The mean difference in the percentage change in PASI was 23.3% (9.8% to 36.8%). In contrast, the RR for clearance at 12 weeks in the patients' and investigators' overall assessment were equal at 7.0 (0.9 to 53.6).

Calcipotriol and cyclosporin - One trial compared calcipotriol and cyclosporin with placebo ointment and cyclosporin in a total of 69 patients

(Grossman *et al.* 1994). The calcipotriol/cyclosporin combination was significantly more effective than placebo/cyclosporin on the basis of the proportion of patients cleared and the percentage change in PASI. At the end of treatment (6 weeks), the RR for clearance in the patients' and investigators' overall assessments were 3.2 (1.1 to 8.7) and 3.9 (1.2 to 12.6), while the mean difference in the percentage change in PASI was 22.1% (7.4% to 36.8%). There were no significant differences in the proportion of patients with marked improvement or cleared lesions; the RR were 1.2 (0.8 to 1.6) and 1.4 (1.0 to 1.9) in the patients' and investigators' assessments, respectively.

5.3.3 Withdrawal from treatment

Table 5.7 summarises the data for withdrawal from treatment for any reason and as a result of adverse effects. The results are expressed as the rate ratio (relative risk, RR) and the rate difference (risk difference, RD). All the pooled rate ratios for withdrawal from treatment have 95% confidence intervals that span unity, indicating that there is no conclusive evidence that patients were more likely to withdraw from using the combined regimen than from using the control intervention. When the withdrawal rates due to adverse effects of treatment were compared, once again the 95% confidence intervals for the rate ratios crossed unity, indicating that patients were no more likely to be withdrawn from using the combined regimen than from using the control. Despite this, indirect comparisons suggest that acitretin is most likely to cause withdrawal while UVB phototherapy is least likely.

Table 5.7 : Comparison of withdrawal rates and risk of adverse effects (95% confidence intervals).

Comparison	Withdrawal (total)	Withdrawal (adverse effects)	Adverse effects (total)	Cutaneous adverse effects	Non-cutaneous adverse effects
Calcipotriol + UVB phototherapy v calcipotriol					
Crude rate	NR	NR	2/20 v 2/20	20/121 v 20/121	0/20 v 0/20
Weighted RR	NR	NR	1 (0.16 to 6.42)	1 (0.57 to 1.76)	1 (0.02 to 48.09)
Weighted RD	NR	NR	0 (-0.19 to 0.19)	0 (-0.09 to 0.09)	0 (-0.09 to 0.09)
Calcipotriol + UVB (3 x week) v placebo + UVB (3 x week)					
Crude rate	0/10 v 0/10	NR	NR	NR	NR
RR	1 (0.02 to 46.06)	NR	NR	NR	NR
RD	0 (-0.17 to 0.17)	NR	NR	NR	NR
Calcipotriol + UVB (2 x week) v placebo + UVB (3 x week)					
Crude rate	14/84 v 15/80	1/84 v 4/80	46/84 v 53/80	NR	NR
RR	0.89 (0.46 to 1.72)	0.24 (0.03 to 2.08)	0.83 (0.64 to 1.06)	NR	NR
RD	-0.02 (-0.14 to 0.10)	-0.04 (-0.09 to 0.01)	-0.11 (-0.26 to 0.03)	NR	NR
Calcipotriol + PUVA v placebo + PUVA					
Crude rate	12/77 v 15/76	1/77 v 4/76	19/64 v 19/63	NR	5/64 v 0/63
Weighted RR	0.79 (0.41 to 1.54)	0.42 (0.08 to 2.29)	0.98 (0.59 to 1.63)	NR	4.59 (0.46 to 45.63)
Weighted RD	-0.03 (-0.14 to 0.08)	-0.04 (-0.10 to 0.03)	0 (-0.13 to 0.12)	NR	0.07 (-0.001 to 0.15)
Calcipotriol + acitretin v placebo + acitretin					
Crude rate	16/76 v 21/59	9/76 v 13/59	74/76 v 56/59	62/76 v 45/59	NR
RR	0.59 (0.34 to 1.03)	0.54 (0.25 to 1.17)	1.03 (0.96 to 1.10)	1.07 (0.90 to 1.28)	NR
RD	-0.15 (-0.30 to 0.01)	-0.10 (-0.23 to 0.03)	0.02 (-0.04 to 0.09)	0.05 (-0.09 to 0.19)	NR
Calcipotriol + cyclosporin v placebo + cyclosporin					
Crude rate	NR	1/35 v 2/34	18/35 v 19/34	13/35 v 9/34	17/35 v 16/34
RR	NR	0.49 (0.05 to 5.11)	0.92 (0.59 to 1.43)	1.40 (0.69 to 2.85)	1.03 (0.63 to 1.69)
RD	NR	-0.03 (-0.13 to 0.07)	-0.04 (-0.28 to 0.19)	0.11 (-0.11 to 0.32)	0.02 (-0.22 to 0.25)

NR : not reported

RR : rate ratio

RD : rate (risk) difference

5.3.4 Adverse effects

There were no significant differences in the proportion of patients experiencing side-effects between the combined regimens and their corresponding control interventions (Table 5.7). In addition, the pooled RR for cutaneous and non-cutaneous adverse effects all had 95% confidence intervals that crossed unity, thereby indicating that patients were no more likely to experience such effects from the addition of calcipotriol. However, the trials evaluated suggest that acitretin was almost three times more likely to cause adverse effects during the randomised treatment than PUVA therapy which was associated with the lowest proportion of patients reporting adverse effects.

5.4 Discussion

Overall, the addition of calcipotriol to several systemic treatments (acitretin, cyclosporin, and PUVA) may produce a small additive therapeutic effect in severe psoriasis without an increase in the incidence of short-term adverse effects. However, the results of the patients' assessment suggest that the magnitude of the effect observed is neither statistically nor clinically meaningful. In other words, a decrease in psoriasis severity reflected in percentage change in PASI, may not be sufficient for the patient to classify the change as a categorical change - for example, from moderate to marked

improvement in response rate ratio as an outcome measure. While the review does not exclude the possibility of small effects in favour of calcipotriol-UVB combinations, there is also insufficient evidence to support the claim that topical calcipotriol enhances the effect of UVB.

5.4.1 Implications of results

Theoretically, any treatment which improved the therapeutic outcome (eg. time, likelihood of clearance) whilst minimising the risks of toxicity would be advantageous. Mostly on the basis of the results of single multi-centre studies, topical calcipotriol has not been shown to substantially enhance the effect of systemic therapy. There were relatively few studies, and it is possible that small additive effects of calcipotriol could have been missed, but the magnitude of the effect observed suggests that the response is not clinically relevant to the patient. A recent review concluded that calcipotriol-UVB combinations were more effective than UVB alone (Koo 1997). This conclusion cannot be verified by these results. The former review included non-randomised studies and the results of primary studies were reported only as significant or not significant with no attempt made to measure effect sizes or pool results.

There was no increase in the incidence of withdrawal rates or side-effects from combined treatment. Given that the adverse effects associated with systemic therapies are mostly dose-dependent, the short duration of these

RCTs are unlikely to detect the most critical side-effects of treatment. Longer trials are needed to establish whether topical calcipotriol improves the risk/benefit ratio by reducing the long-term risks of toxicity.

Is there a dose-sparing effect? It appears that combination therapy can decrease the cumulative exposure to systemic therapy. Recent reports suggest that calcipotriol can reduce the number of UVB exposures and the cumulative energy density (Ramsay 1998). Other studies have shown significant reductions in the cumulative exposure to UVA (Frappaz & Thivolet 1993) and acitretin (van de Kerkhof *et al.* 1998). As yet, the clinical relevance of the amount of energy density saved has not been determined; however, from a theoretical point of view less ultraviolet exposure is likely to cause fewer ultraviolet related side effects. Likewise, lowering the daily dose of systemic drugs would be likely to result in a reduction in their dose-dependent adverse effects. This could also result in considerable savings in time and total costs.

Does topical calcipotriol prolong the duration of remission? The studies were not numerous enough for this analysis; only four trials reported on relapse rates during post-treatment follow-up. Each trial used different relapse criteria and varied lengths of post-treatment follow-up. These factors limit the degree to which the results can be compared and preclude the drawing of firm conclusions about the long-term efficacy of any of the interventions studied. Nevertheless, on the basis of the limited data available, the combination regimens do not appear to reduce the frequency of relapse.

Since psoriasis is a chronic disease for the majority of sufferers, differences in remission time following treatment may be a more important measure of a treatment's relative efficacy than differences in the clearing capacity. As discussed previously (see section 2.4), the time to relapse would be a useful outcome measure, but the definition of relapse would need to be precisely defined and universally agreed on so that the results of different trials can be directly compared.

Other topical agents besides calcipotriol have also been shown to be effective adjuvant therapies in severe psoriasis. In practice, coal tar and topical corticosteroids are routinely used with many systemic therapies (Katz 1997). Traditionally, coal tar has been used in combination with UVB phototherapy in the Goeckermann regimen. In recent years, dithranol (Storbeck *et al.* 1993), tacalcitol (Kokelj *et al.* 1996) and tazarotene (Foster *et al.* 1998) have been reported to improve the outcome of second-line treatments and their risk/benefit profile should be compared with that of calcipotriol.

5.4.2 Limitations of study

Publication bias is a potential threat to the validity of any systematic review. Although strenuous efforts were made to locate all RCTs, many of the conclusions were drawn from single studies. Moreover, not all the trials reported on the outcomes of interest. Therefore, to obtain the pooled estimates the trials included in the different analyses do not necessarily match. For

example, it was impossible to extract data on withdrawal rates from five trials which conducted bilateral (right/left) comparisons.

The PASI was selected as an outcome measure in this analysis for several reasons. Firstly, it was the most commonly used outcome measure in the trials. Secondly, most of the trials collected data on a number of outcomes, and as such there is the potential for bias due to the selective publication of results showing impressive treatment effects. Since PASI scores were obtained for all but two of the included trials, the likelihood of bias due to selective publication of outcomes is minimal. However, it is important to acknowledge that the PASI has several major problems and recognise that the results must be interpreted with caution (see section 2.3.3).

5.5 Conclusions

Evidence for some superiority of the combinations over systemic treatment alone was obtained. The acitretin, cyclosporin and PUVA combinations showed statistical significance in the difference in PASI from baseline. However, this is not translated into an increase in the number of patients who achieve marked improvement or clearance. It has previously been suggested that topical calcipotriol enhances the effect of UVB phototherapy (Koo 1997). In the studies which met our inclusion criteria, a beneficial effect over and above that of UVB irradiation alone was not detected.

In practice, the cumulative exposure to systemic agents is substantial, increasing the lifetime risk of serious toxicity. There is some evidence that topical calcipotriol can reduce the cumulative exposure to systemic treatments and thereby potentially lower the risks of toxicity. The combination treatments did not result in aggravation or increased frequencies of short-term adverse effects. However, much longer clinical trials are warranted to identify the long-term efficacy and safety profile of the various combination therapies. Specifically, there is a need to compare the clearing capacity, post-treatment remission, safety and the cost for these alternatives over a more realistic follow-up period (for example, a year). If the effects are significant and worthwhile, then combination therapies should be considered when practice guidelines are defined.

CHAPTER 6

Cost-effectiveness analysis of calcipotriol versus short-contact dithranol in the treatment of plaque psoriasis

6.1 Introduction

The morbidity associated with psoriasis is well documented in terms of impact on quality of life. Economic considerations are also important in health services which have limited budgets. Psoriasis presents a chronic and recurrent drain on healthcare resources. In the US, the total cost of psoriasis care has been estimated at \$3.2 billion per year (Sander *et al.* 1993). It affects 1-2% of the population in the UK and accounts for approximately 8% of referrals to dermatology departments (Cork 1993). Not only are there costs associated with treatment, but psoriasis also imposes a financial burden on the patients themselves in terms of loss of earnings, travel expenses to the doctor/hospital, prescription costs, and the use of non-prescription or complementary medicines. Traditionally, these indirect costs of the condition have been little quantified in practice.

In Chapter 4, it has been shown that calcipotriol is more effective than many of its competitor topical therapies for the short-term management of mild-to-moderate plaque psoriasis and is generally well tolerated by patients.

However, the major disadvantage of calcipotriol is its cost (£8.15 per 30g tube compared with £1.40 for betamethasone 0.1% valerate) (BNF March 1999). In any pharmacoeconomic evaluation for psoriasis, the duration of remission is also an important consideration. Psoriasis is a chronic disease for the majority of sufferers, and therefore relapse results in additional costs for further treatment.

Objective

The aim of this study was to examine how small differences in efficacy affect the comparative cost-effectiveness of treatment. In particular, the analysis assesses whether the added effects of topical calcipotriol represent an incremental improvement that justifies the additional expense.

6.2 Methodology

6.2.1 Perspective and time horizon

The perspective of this pharmacoeconomic study is that of the NHS as payer. In order to compare costs and consequences meaningfully, the interventions were compared using two analytic horizons : a short-term horizon (12 weeks) that includes only primary data derived from RCTs, and a longer-term horizon (up to 1 year) that also incorporates modelled data.

6.2.2 Treatment comparator

Dithranol has been used for over 50 years and remains an effective and extensively used topical therapy. In general practice, it is primarily used in a short-contact regimen and therefore this was chosen as the comparator in this study.

6.2.3 Selection of effectiveness measures (end point)

The degree of improvement in psoriasis (i.e. marked improvement or cleared lesions) as judged by the patient, is selected in the present analysis to be the outcome measure by which the effectiveness of the treatments will be compared.

6.2.4 Decision analysis

Decision tree

Two decision analysis models were used to compare the cost-effectiveness of calcipotriol and “short-contact” dithranol. In the first model (Figure 6.1, Model 1), a short-term horizon (12 weeks) was used where a choice of primary treatment is made (calcipotriol or dithranol) and possible downstream events include initial “success” or “failure”. In the second model (Figure 6.2,

Model 2), a longer horizon (up to 1 year) was examined. Following an initial success, it was assumed that patients could either sustain the response (no relapse), which would lead to cessation of topical treatment, or experience a recurrence of symptoms (relapse), in which case the patient is re-treated with the primary drug. If re-treatment fails, the patient is then switched to treatment with the comparator. If the comparator drug is not effective (failure), the model terminates as the patient is assumed to require more intensive or an alternative treatment which is outside the threshold of this analysis.

Primary treatment failure results in treatment with the comparator drug (secondary treatment). If this treatment fails, the patient is assumed to require more intensive treatment, and the model terminates. Secondary treatment success can either be followed by relapse, in which case the patient is retreated with the comparator drug, or no relapse, which would result in cessation of treatment and subsequent termination of the model. Likewise, if re-treatment succeeds, the model terminates and the treatment is stopped. On the other hand, if re-treatment fails the model terminates as the patient is assumed to require more intensive therapy.

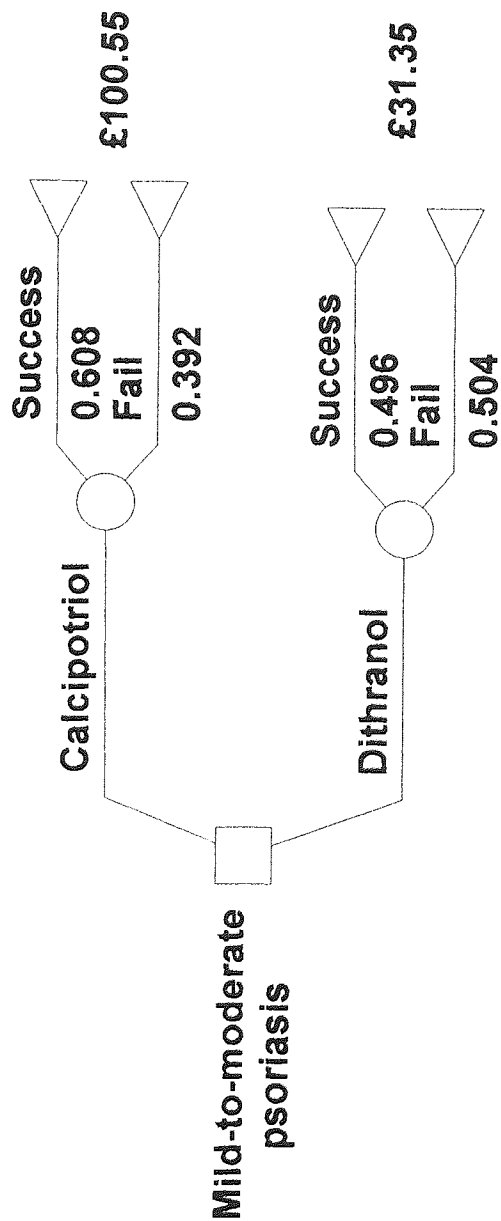


Figure 6.1 : Model 1: Decision analytic model showing the cost and efficacy for 12 weeks of therapy of calcipotriol compared with short-contact dithranol as primary treatments. The estimated treatment costs for each comparator are shown at the right side of the tree.

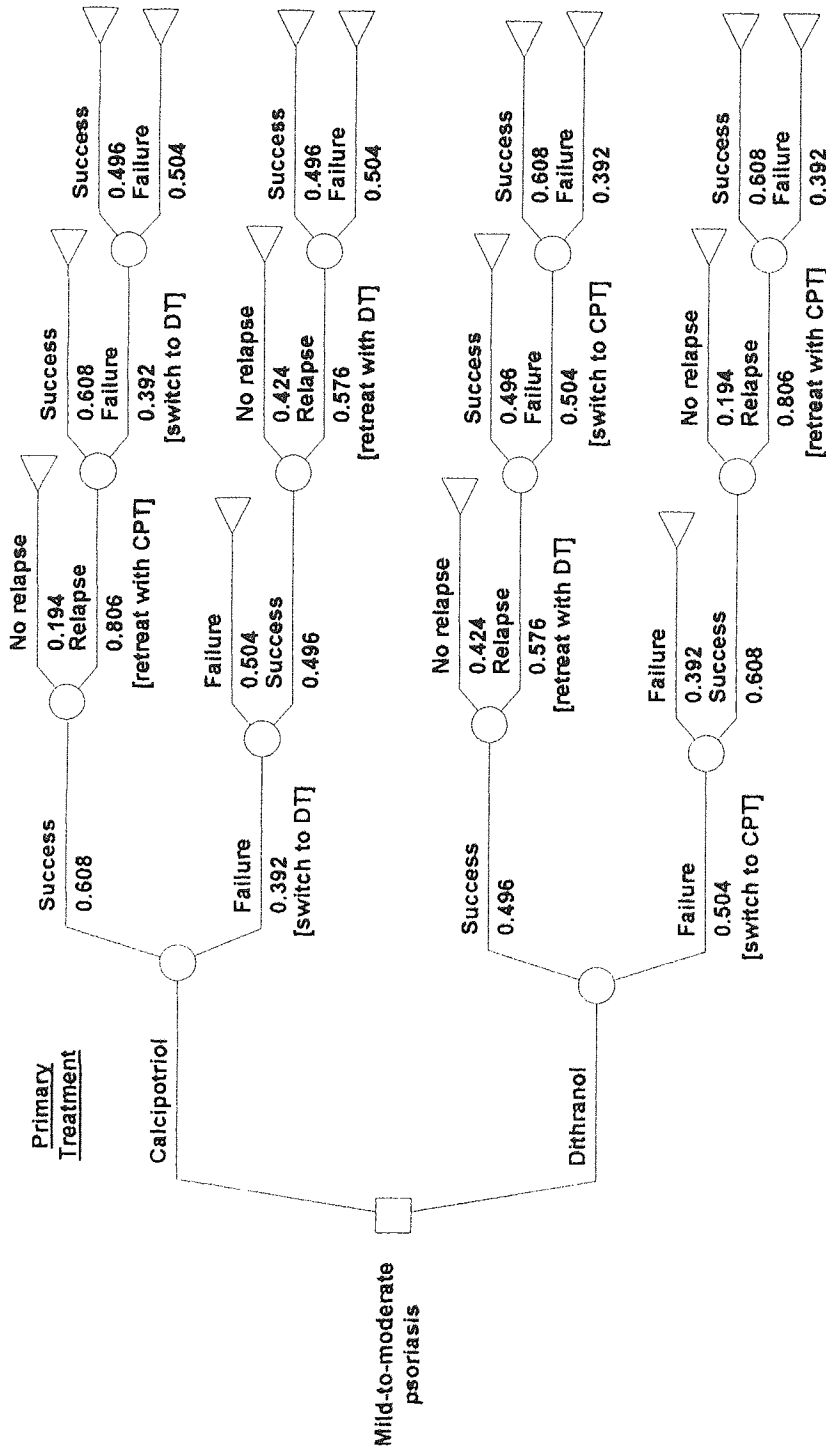


Figure 6.2 : Model 2: Decision analytic model comparing calcipotriol and short-contact dithranol for the long-term treatment of patients with mild-to-moderate plaque psoriasis. [CPT : calcipotriol; DT : short-contact dithranol].

Treatment “success” was defined as the proportion of patients who experienced a marked improvement or clearing of lesions (i.e. $\geq 75\%$ improvement from baseline) which was based on the following 5-point patient-rated scale : completely cleared, marked improvement, some improvement, no change, and worse. The treatment “failure” rate is the complement of the treatment success rate (i.e. $1 - \text{success rate}$). “Relapse” was defined as a change from the end of treatment of three grades or more in the investigator’s global assessment of response.

6.2.5 Assumptions

The following assumptions underlie the analyses conducted :

- 1 The effectiveness of treatment is not affected by prior treatment with either drug.
- 2 The RCTs of calcipotriol versus Dithrocream® did not examine relapse rates as an outcome. Therefore, relapse rates available for Micanol® would be used in this analysis to represent short-contact dithranol (Lister *et al.* 1997).
- 3 Once daily dithranol was compared against twice daily calcipotriol. It was therefore assumed that the quantity of dithranol that was used would be equivalent to half the mean quantity of calcipotriol.
- 4 In calculating drug acquisition costs, Dithrocream®2% was used to estimate the cost of the short-contact dithranol regimen.

6.2.6 Sources of clinical data

Table 6.1 shows the probabilities of success and relapse which were used in the models and the source of the estimates. Notably, a recently published head-to-head randomised controlled trial of calcipotriol versus “short-contact” dithranol (12 weeks duration) was used to extract the efficacy data (Wall *et al.* 1998).

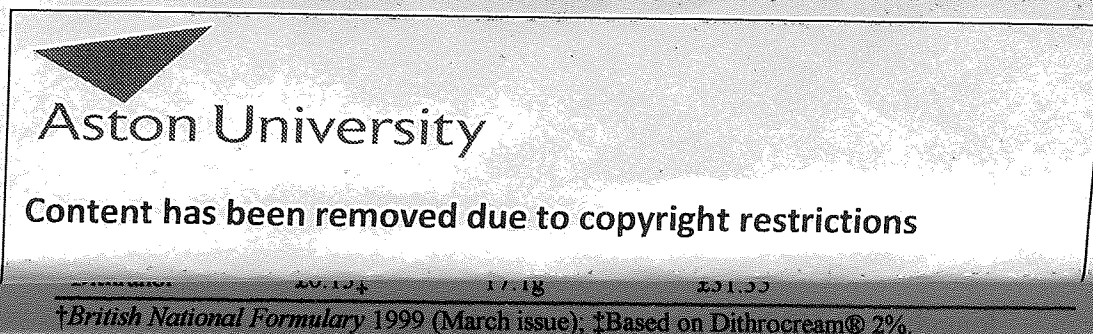
Table 6.1: Probability estimates for success and relapse used in the decision analytic models.

<i>Topical drug</i>	<i>Variable</i>	<i>Probability</i>	<i>Source</i>
Calcipotriol	Success	0.608	Wall <i>et al.</i> (1998)
	Relapse	0.806	Lister <i>et al.</i> (1997)
Dithranol	Success	0.496	Wall <i>et al.</i> (1998)
	Relapse	0.576	Lister <i>et al.</i> (1997)

6.2.7 Cost elements

As the pharmacoeconomic analysis was conducted from the perspective of the prescriber, only the direct costs of treatment were included in this study (Table 6.2).

Table 6.2 : Estimated costs for drug regimens.



Unit costs were based on the cost of NHS drug treatments from the 1999 *British National Formulary* (March issue). The costs of physician consultations and dispensing fees were not included as these costs are common to both interventions and will therefore be incurred irrespective of the treatment selected. No direct, indirect or intangible costs that accrue to patients or to any other entity other than the NHS is considered.

6.2.8 Sensitivity analysis

A one-way sensitivity analysis was performed by varying the efficacy and cost estimates to identify the most important variables affecting the cost-effectiveness of the strategies. The measures varied for sensitivity analysis were:

Efficacy The results reported by Berth-Jones *et al.* (1992) were used, i.e.
- the success rate of calcipotriol is 0.784 (instead of 0.608 in the baseline case)

- the success rate of dithranol is 0.542 (instead of 0.496 in the baseline case).

Cost estimate The average drug costs per patient estimated by Harrington *et al.* (1995) were used, i.e.

- the costs were £100 for calcipotriol and £36 for dithranol (instead of £100.55 and £31.35, respectively).

6.3 Results

6.3.1 Base case analysis

The cost estimates to treat a patient with topical calcipotriol or short-contact dithranol for 12 weeks are shown in Table 6.2. Model 1 assessed the cost and efficacy of 12 weeks treatment with either agent as sole therapy. The differences in drug acquisition costs and success rates are shown in Table 6.3.

Table 6.3 : Model 1: Differences in drug acquisition cost and success rates (12 week horizon).

<i>Topical drug</i>	<i>Cost (£)</i>	<i>Success rate</i>	<i>Incremental cost</i>	<i>Incremental success</i>	<i>Incremental C/E ratio (£/success)</i>
Calcipotriol	£100.55	0.608	£69.20	0.112	£617.86
Dithranol	£31.35	0.496	-	-	-

Calcipotriol is the most effective treatment (60.8% success), but it is also the most expensive (£100.55 per patient treated). Compared with short-contact dithranol, each incremental success that calcipotriol achieves costs £617.86.

In Model 2, primary treatment failure or relapse increased the costs of both strategies particularly for short-contact dithranol which was the least expensive treatment in model 1. Interestingly, for the regimen using short-contact dithranol as first line treatment, failure or relapse ultimately resulted in treatment with calcipotriol which evoked the highest drug acquisition cost. The strategy of calcipotriol as first line treatment still had the highest expected cost per successful treatment. However, the incremental cost using this strategy is now £41.35 compared with short-contact dithranol (Table 6.4).

Table 6.4 : Model 2: Differences in drug acquisition cost and success rates (long-term horizon).

<i>Topical drug</i>	<i>Estimated cost</i> (£)	<i>Efficacy rate</i> (success or no relapse)	<i>Incremental cost</i>
Calcipotriol	£171.65	0.649	£41.35
Dithranol	£130.30	0.649	-

In terms of cost per successful day's treatment (i.e. the cost for a day in which the patient reported a marked improvement or cleared lesions), the regimen of calcipotriol as first line treatment is the most effective strategy (116 successful days); it is also the most expensive (£171.65 per patient). The incremental cost per successful day's treatment is £21.39 compared against dithranol (Table 6.5).

Table 6.5 : Model 2: Incremental cost per successful day (long-term horizon).

<i>Topical drug</i>	<i>Estimated cost (£)</i>	<i>Estimated efficacy</i> (successful days [†])	<i>Incremental cost</i>	<i>Incremental efficacy</i>	<i>Incremental C/E ratio</i> (£/successful day)
Calcipotriol	£171.65	116.32 days	£41.35	1.94 days	£21.39
Dithranol	£130.30	114.38 days	-	-	-

†[success rate x treatment duration (days)]

6.3.2 Sensitivity analysis

The sensitivity of the base case estimates was tested varying the efficacy and costs of the regimens in Model 1. The results are shown in Table 6.6.

Table 6.6 : Sensitivity analysis of Model 1 assessing cost-effectiveness of topical therapies for mild-to-moderate psoriasis (12 week horizon).

<i>Variables and range</i>	<i>Base case estimate</i>	<i>Incremental C/E ratio (£/success)</i>
Base case estimate	-	£617.86
Success rate		
Calcipotriol 0.784	0.608	£240.28
Dithranol 0.542	0.496	£1048.48
Cost		
Calcipotriol £100	£100.55	£612.95
Dithranol £36	£31.35	£576.34

In all cases, short-contact dithranol was more cost-effective than topical calcipotriol. In Model 1, assuming the higher success rates of 0.784 for calcipotriol, the incremental cost per success for calcipotriol is now £240.28 compared against dithranol. If the success rate of dithranol is 0.542, then the incremental cost per success for calcipotriol is £1048.48 compared against dithranol. Adjusting the cost of treatment (£100 for calcipotriol and £36 for dithranol), did not substantially change the comparative cost-effectiveness of the treatment strategies.

6.4 Discussion

Given the rising pressures on health care budgets, it is becoming increasingly important to provide evidence of value for money in the selection and use of treatments. The comparative cost-effectiveness of various topical regimens for treating chronic plaque psoriasis is not clear. A clinical trial to evaluate this would be difficult and expensive as it would require large numbers of patients and long-term detailed follow-up. Decision analysis techniques therefore provide valuable guidance in situations where trial data is unavailable and difficult to obtain. From the perspective of the prescriber, the results of this study have shown that short-contact dithranol is more cost-effective than topical calcipotriol in the treatment of mild-to-moderate plaque psoriasis.

6.4.1 Implications of the results

Topical therapies are the most widely used treatments for mild-to-moderate psoriasis, and information on relative cost-effectiveness for the various agents has until recently received limited attention. Overall, from the prescriber's perspective, these results have shown that even if a new treatment is shown to be marginally better than an older conventional treatment, the difference in cost can make a large difference in the cost-effectiveness and hence the direct cost to the prescriber. In particular, choosing treatment on the basis of

clearing capacity alone does not identify the most cost-effective regimen.

Given the assumptions, selecting short-contact dithranol as first-line treatment was the most cost-effective approach despite being slightly less effective than calcipotriol in terms of clearing capacity. This is because the drug acquisition cost of calcipotriol is substantially higher than that of short-contact dithranol and patients were more likely to achieve a longer remission period following treatment with dithranol. In other words, the longer the time horizon, the more costly it is to the NHS to treat mild-to-moderate psoriasis by selecting topical calcipotriol as first-line treatment than it is to select dithranol as first-line and bearing the risk of switching therapy if the symptoms worsen. When the time horizon is very short, i.e. up to 3 months, it is also less costly to the NHS to select short-contact dithranol rather than use topical calcipotriol.

In contrast, an earlier evaluation reported that calcipotriol proved a more cost-effective therapy (Harrington 1995). However, the results cannot be verified by this analysis. The former evaluation considered only short-term outcomes with no attempt made to examine the potential impact of relapse. Re-analysing Model 1 as part of a sensitivity analysis using selected variables from the earlier study did not substantially alter the conclusions reached. Based on the results of the sensitivity analysis, the conclusions were not heavily dependent on the precise estimates of effectiveness.

6.4.2 Limitations of the study

There are limitations to the cost-effectiveness conclusions reached as they rely on reprocessed data rather than information gathered prospectively from patients. The results do not apply directly to individual patients and cannot be extrapolated to consider recalcitrant forms of psoriasis. Therefore, the cost-effectiveness of systemic treatments and combination regimens is beyond the scope of this analysis. Nevertheless, the results apply to treatment with topical therapies for a duration of up to 1 year. At policy-making level, the probabilities obtained from the randomised controlled trials will represent the likely outcomes from treatment within a population of patients with mild-to-moderate psoriasis.

In practice, many other factors—for example the potential for adverse effects, previous response to treatment and patient preference—will also play an important role in the selection of treatment. Quality of life issues also need to be considered. The perspective that has been taken in this study is that of the NHS as provider. Therefore, only the direct costs of treatment to the NHS have been estimated and used in the derivation of cost-effectiveness ratios. If a societal or patient perspective had been used, indirect cost (losses in productive capacity) and intangible cost (social and emotional costs) would have had to be considered.

This study did not attempt to introduce health-related quality of life

information into the analysis. Although previous studies have shown that psoriasis has an adverse impact on patients' quality of life, a recent randomised study of 306 patients showed that there were no significant differences in the total mean scores for the Psoriasis Disability Index and the Sickness Impact Profile between topical calcipotriol and short-contact dithranol (Wall 1998). There were also no significant differences between treatments in the change in personal expenditure, travel expenses to doctor/hospital, prescription costs, costs of non-prescription/alternative medicines, cosmetics, laundry bills/dry cleaners, and expenditure by relatives or friends.

6.5 Conclusions

The decision analysis models have shown that from the prescriber's perspective the relatively small differences in efficacy between calcipotriol and short-contact dithranol lead to large differences in the direct cost of treating patients with mild-to-moderate plaque psoriasis. In this study, choosing treatment on the basis of clearing capacity alone did not identify the most cost-effective regimen. Accordingly, using calcipotriol as second-line treatment to dithranol was the most cost-effective strategy. The results suggest that selecting short-contact dithranol as first-line treatment might not only help contain costs but also improve outcomes in terms of more durable remission following treatment. Further research is needed to examine the clinical and economic issues affecting patients under treatment for psoriasis

in the UK. In particular, the maintenance value of the various treatment strategies, including combination therapies, and the assessment of patient's preferences has not yet been adequately addressed for this chronic recurring disease.

CHAPTER 7

General Discussion

As the pathophysiology of psoriasis undergoes more detailed unravelling and as understanding of the biochemical basis of psoriasis deepens, so does our knowledge of the mode of action of antipsoriatic drugs. Advances in pathophysiology represent a major step forward, for example, the role of T lymphocytes in relation to the antipsoriatic effects of cyclosporin. Yet, current drug treatments are often only partially effective and further developments are awaited. Surprisingly though, uncertainty still remains when we try to explain the mechanism of action of many antipsoriatic drugs.

Thus while the efficacy of treatments such as calcipotriol and methotrexate has universal acceptance, there are many features of those and similar antipsoriatic agents that we still do not understand. For example, the mechanism of action of dithranol has yet to be fully defined while the reasons why some forms of psoriasis respond better to treatment than others is not completely understood. The recent discovery of various genes linked to psoriasis susceptibility has contributed to improving our knowledge in this area but much remains to be unravelled.

Psoriasis is a variable and often unpredictable skin condition which may involve any part of the skin surface producing a multiplicity of symptoms. These factors, together with a tendency to spontaneous remission, make it difficult to evaluate therapeutic interventions and there is a paucity of appropriate clinical outcome measures. A wide range of techniques have been used to evaluate the severity of the disease and its response to treatment. This has resulted in a lack of standardisation, which complicates the direct comparison of results and ultimately the pooling of outcomes from different clinical trials.

Many of the existing scales were developed for use in specific trials and limited attention has been paid to the reliability, sensitivity and validity of such measures. Generally, the physical signs such as erythema, induration and desquamation are rated as individual sign scores or incorporated into pooled indices such as the PASI. However, major problems arise in how to weight the different signs of the disease to produce a summary score which reflects the severity of the disease meaningfully for the patient and clinician. In practice, the contribution which each sign makes to an overall summary score, such as the PASI, has been assigned arbitrarily.

Ideally, a core set of reliable and validated outcome measures for use in all psoriasis clinical trials is needed. Objective instrumental methods should minimise observer variation, but unless a simple non-invasive method can be developed, the uptake of such technology will probably be limited by cost and

lack of practicality. Moreover, the translation of instrumental readings into clinically relevant measures is always a major problem, and for none of the methods has there been a robust mapping of instrumental readings on to a clinically meaningful scale.

Further research is needed to determine the most appropriate and sensitive parameters when measuring drug efficacy in psoriasis. The duration of remission is an important factor in the therapeutic decision which has received minimal attention within the time-frame of the usual clinical trials. In particular, topical treatments have been evaluated only in the short-term, while their maintenance value has not yet been adequately addressed. There is no cure for psoriasis, therefore the majority of patients will relapse despite achieving an initial response to treatment on the basis of clearing capacity. If relapse rates were to be measured in clinical trials, then the definition of relapse would have to be clearly defined and universally agreed on so that the results of different clinical trials can be directly compared.

It is now widely acknowledged that the personal burden of psoriasis cannot be described fully by parameters of disease activity such as the degree of erythema or plaque thickness. In recent years, there has been a shift in focus to determining QoL. A number of QoL instruments have been developed which facilitate a wider examination of the burden of the disease and the effects of treatment on the sufferer's quality of life. It is of particular interest that the PASI does not show a significant correlation with the Sickness Impact

Profile, a widely used generic QOL instrument (Finlay *et al.* 1990).

Although the importance of quality of life is broadly acknowledged, questions remain as to how QoL should be measured and implemented in clinical trials and routine practice. The confusion is increased by the different ways in which the instruments have been developed, the categories and items included, and the methods by which their reliability and validity have been examined. Increasingly, practitioners are faced with the task of selecting a suitable instrument from a range of competing alternatives which may ultimately yield different results. Further head-to-head comparisons of measures is needed in order to guide investigators in their choice of instrument.

The treatment of psoriasis can be difficult and disappointing, despite the availability of a number of treatment options. Psoriasis is a chronic condition and often difficult to treat due to its sporadic course, variable response rates to treatments, and their unacceptable adverse effects. Considerable uncertainty exists as to the optimal treatment for mild-to-moderate psoriasis. There is no well-defined approach to long-term management, current guidelines review the various treatment options but do not clearly define a stepped approach for the management of patients.

Topically applied medications remain the cornerstone of therapy for mild-to-moderate psoriasis. Interest first arose in the use of vitamin D analogues with

the serendipitous observation that a patient's psoriasis improved dramatically while their osteoporosis was being treated with 1α -hydroxy-vitamin D₃ (Morimoto & Kumahara 1985). Since that time calcipotriol has become one of the most widely prescribed treatments for psoriasis.

The results of the meta-analysis reported herein show that calcipotriol is an effective antipsoriatic agent. In the short-term, the pooled data found calcipotriol to be more effective than calcitriol, tacalcitol, coal tar and short-contact dithranol. Only potent topical corticosteroids appeared to have comparable efficacy at 8 weeks, with less short-term side-effects than calcipotriol. Potent topical corticosteroids also added to the antipsoriatic effect of calcipotriol, but moderate corticosteroid agents did not. One unexpected observation in the studies reviewed is that indirect comparisons suggest that calcipotriol is more effective in adults than children. This justifies further investigation because of the sparsity of studies using calcipotriol in children.

All of the topical drugs reviewed appear to be quite safe in terms of short-term safety assessable within the time-frame of the usual clinical trials. Calcipotriol results in skin reactions in over 17% of the time, usually mild but which can occasionally lead to discontinuation of treatment. Concomitant therapy with a topical corticosteroid appears to suppress the occurrence of calcipotriol-induced irritation. The magnitude of the effect is related to the potency of the corticosteroid, and is probably explained by their anti-

inflammatory mode of action. Although calcipotriol caused more skin irritation than topical corticosteroids, this has to be balanced against the potential long-term effects of the latter.

Dithranol caused more lesional irritation than calcipotriol, but facial or scalp irritation occurred less frequently. Unfortunately, there was insufficient data to determine whether the newer dithranol formulations were any less irritant than the more established products. Longer term comparative trials of calcipotriol versus dithranol and topical corticosteroids are needed to see whether these short-term benefits are mirrored by long-term outcomes such as duration of remission and improvement in quality of life.

Overall, calcipotriol was not an effective adjuvant treatment with systemic therapies on the basis of patients' assessments of response. There is insufficient evidence to support any strong or large effects in favour of improvements in efficacy with this form of combination treatment. Although the antipsoriatic effects of acitretin, cyclosporin and PUVA phototherapy were enhanced with the addition of topical calcipotriol using the PASI as outcomes, this is not translated into an increase in the number of patients who achieve at least marked improvement. Yet, the occasional report of additive antipsoriatic effect continues to appear in the literature and we therefore need to revisit this as new evidence becomes available.

Over the short duration of the trials, there were no significant differences in

withdrawal rates or adverse effects between the combination regimens and systemic treatments used alone. There was a total absence of long-term morbidity data on the effectiveness of any of the combinations studied. Nevertheless, there is some evidence to suggest that calcipotriol may reduce the cumulative exposure to systemic therapies to obtain clearance. Given that the most serious side-effects of systemic treatments are dose-dependant, treatment strategies that reduce the total exposure to systemic therapies would be advantageous. This could also result in savings in overall treatment costs. Longer-term trials are needed to determine whether the addition of topical calcipotriol to systemic therapy improves the risk/benefit ratio by reducing the long-term risk of toxicity. Equally important is the need to examine the impact of such combinations on the duration of remission following treatment.

The comparative cost-effectiveness of various topical regimens for treating mild-to-moderate psoriasis is not clear. As there is a number of treatment regimens, of differing costs, there is a need for a rational basis from which to make a choice. A clinical trial to evaluate this would require a large number of patients and long and detailed follow-up. Decision analysis therefore provides useful information and guidance in situations where trial data is unavailable or difficult to obtain. The variables used in the analysis reported herein are consistent with the findings of randomised controlled comparisons of calcipotriol against short-contact dithranol.

Using the decision analysis models, from the prescriber's perspective, small differences in efficacy can lead to large differences in the comparative cost-effectiveness of topical treatments for plaque psoriasis. The analysis also shows how strongly subsequent management of patients who relapse influences the comparative cost-effectiveness of treatment strategies. Treating all patients with calcipotriol as first line agent greatly increases the direct costs of treatment. The results suggest that selecting short-contact dithranol as first-line treatment was the most cost-effective strategy. Further research is needed to examine the maintenance value of the various treatment strategies, including combination therapies, and the assessment of patient's preferences has not yet been adequately addressed for this chronic recurring disease.

In all, the selection of topical treatments for chronic plaque psoriasis should be more rationalised by using these results. RCTs have found that calcipotriol improves plaque psoriasis in the short-term. It appears to be more effective than coal tar, tacalcitol and short-contact dithranol, and at least as effective as potent topical corticosteroids. There was little evidence on the value of maintenance treatment and the duration of remission for any of the interventions studied. However, the major disadvantage of calcipotriol is its cost. Thus, the choice of calcipotriol alone as a first-line treatment must be re-evaluated based on the results of this analysis. The main issue, however, is still the necessity for RCTs with an appropriate duration of follow-up for the estimation of the long-term efficacy and the cost/benefit ratio for the various treatment strategies.

APPENDIX I

Reports of randomised controlled trials (RCTs) of topical calcipotriol :

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APPENDIX II

RCTs of calcipotriol used in combination with phototherapy or systemic therapies :

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