

Executive summary

A systematic review of treatments for severe psoriasis

CEM Griffiths¹ *

CM Clark¹

RJG Chalmers¹

A Li Wan Po²

HC Williams³

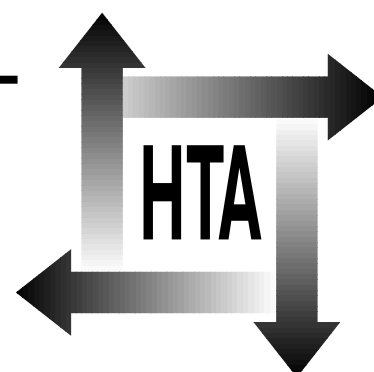
¹ Dermatology Centre, Hope Hospital, University of Manchester School of Medicine, Salford, UK

² Centre for Evidence-Based Pharmacotherapy, Aston University, Birmingham, UK

³ Department of Dermatology, Queens Medical Centre, University of Nottingham, UK

* Corresponding author

**Health Technology Assessment
NHS R&D HTA Programme**





Executive summary

Objectives

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

Methods

Data sources

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

Study selection and assessment of validity

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

Data extraction

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

Data synthesis

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

success rate differences and displayed as forest plots. When homogeneity across trials could be demonstrated, pooled rate differences are also shown.

Results

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

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

Cyclosporin

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

Retinoids

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

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

Methotrexate

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

Photochemotherapy and phototherapy

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

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

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

Combination treatment using phototherapy or photochemotherapy with a vitamin D₃ analogue (e.g. calcipotriol) was more effective than either treatment alone. Phototherapy or photochemotherapy combined with a topical steroid was also more effective than either treatment alone.

Hydroxyurea

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

Fumarates

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

Azathioprine

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

Sulphasalazine

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

Costs and cost-effectiveness

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

Conclusions

Implications for healthcare

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

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

- cyclosporin
- systemic retinoids (acitretin and etretinate), especially in combination with PUVA
- photochemotherapy and phototherapy (PUVA, broadband UVB and narrowband UVB)
- combinations of topical vitamin D₃ analogues and topical steroids with either photochemotherapy or phototherapy
- fumarates.

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

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

Recommendations for further research

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

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

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

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

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

Publication

Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC. A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000;**4**(40).

NHS R&D HTA Programme

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

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

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

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

The research reported in this monograph was funded as project number 96/16/02.

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

Criteria for inclusion in the HTA monograph series

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

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

HTA Programme Director:	Professor Kent Woods
Series Editors:	Professor Andrew Stevens, Dr Ken Stein, Professor John Gabbay
Monograph Editorial Manager:	Melanie Corris

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

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
<http://www.ncchta.org>

ISSN 1366-5278