A systematic review of treatments for severe psoriasis
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Authors' objectives
To compare the effectiveness of currently available treatments for severe psoriasis, and to identify the areas in need of further research.

Searching
MEDLINE (from 1996 to June 1999) and EMBASE (from 1980 to June 1999) were searched. The search strategy used subject headings such as 'psoriasis', 'treatment', 'psoriasis-drug-therapy' and 'clinical trial', textwords including 'study', 'trial*', and 'random*'; and the title words 'clinical-trial' or 'compar*'. The results of the search were cross-checked against the Cochrane Controlled Trials Register. In addition, the Science Citation Index and the European Dermato-Epidemiology Network trials register were searched. Further studies were identified by examining conference proceedings (e.g. Psoriasis From Gene to Clinic, and the International Psoriasis Symposium), by contacting the manufacturers of relevant drugs, and by handsearching relevant journals. A prior review of trials of methotrexate was used to find studies conducted before 1966.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. One of the included studies consisted of six arms to which patients were randomly allocated, and one arm to which consecutive patients were allocated. Only data relating to those patients randomised to a treatment were included in this review.

Specific interventions included in the review
The authors appeared to consider studies of any design for inclusion in the review. The interventions studied included: cyclosporin (CSA; 1.25 to 14 mg/kg) compared with placebo or etretinate (0.5 to 0.75 mg/kg); etretinate (1 mg/kg or 50 mg total dose) alone or combined with psoralen plus ultraviolet A irradiation (PUVA), compared with placebo; acitretin (10 to 75 mg alone) alone or combined with PUVA, compared with placebo or etretinate (30 to 50 mg); methotrexate (no doses given); phototherapy using broadband (290 to 320 nm) or narrowband (311 nm) ultraviolet B (UVB) radiation; photochemotherapy (long-wave PUVA irradiation at 320 to 400 nm); hydroxyurea (1.0 g/day) compared with placebo; fumaderm (up to 6 doses per day) compared with placebo; octyl hydrogen fumaric acid ester (MAFAE)-magnesium salt (5 mg), or MAFAE-zinc salt (3 mg); MAFAE-sodium salt (60 to 240 mg) compared with placebo; dimethylfumaric acid ester (60 to 240 mg) compared with placebo; azathioprine (no doses given); and sulphasalazine (3 to 4 mg) compared with placebo.

Participants included in the review
Psoriasis. To be included in the review, the studies had to have investigated interventions for moderate to severe chronic plaque psoriasis. However, studies which pertained only to palmoplantar pustular psoriasis, gutatate psoriasis or psoriatic arthritis were excluded. The review included studies of treatments for those with active psoriasis and for those whose psoriasis was in remission.

Outcomes assessed in the review
There were no inclusion or exclusion criteria relating to the outcomes of interest. The efficacy of the interventions in the included studies was addressed in relation to a number of success criteria. These included: a reduction in the symptoms ('Clear or almost clear'); a specified percentage reduction in the Psoriasis Area and Severity Index or the Psoriasis Severity Index; the response rate difference; a reduction in the proportion of the total body surface area affected; Likert scores; and subjective reports by patients.

How were decisions on the relevance of primary studies made?
Two reviewers made decisions about the relevance of the studies.
Assessment of study quality
The trials were considered to be valid if they met the inclusion criteria and if they supplied sufficient data for further analysis. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Data concerning all outcomes of interest were extracted from all eligible studies and entered into spreadsheets. The authors do not state how many of the reviewers performed the data extraction, or whether any cross-checking process was undertaken.

Methods of synthesis
How were the studies combined?
Success rate differences were displayed as forest plots. When no heterogeneity across trials was demonstrated, the rate differences were pooled using a fixed-effect model.

How were differences between studies investigated?
Differences between the studies were investigated using the Q statistic and 95% confidence intervals were calculated. Sources of heterogeneity were discussed in the text of the review.

Results of the review
The review included 95 RCTs, a number of which compared more than one intervention. A total of 5,663 patients were recruited by the studies.

Eighteen RCTs investigated CSA (n=2,350). Of these, 13 (n=1,688) concerned the induction of remission in patients with active disease and 5 (n=662) concerned the maintenance of remission. Thirty-three RCTs (n=2,419) compared the use of oral retinoids with either each other, another intervention or placebo. Fifty RCTs (n=2,876) compared the use of phototherapy and photochemotherapy with either other phototherapy or photochemotherapy regimes, another intervention or placebo. Four studies (n=258) examined the use of fumarates, and there was one study each of hydroxyurea (n=166) and sulphasalazine (n=188); all 6 of these studies enrolled only patients with active disease.

No RCTs were found that investigated the use of methotrexate or azathioprine in the treatment of psoriasis.

There was considerable heterogeneity within each intervention group. The sources of heterogeneity included 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 according to the skin type. Drug formulation and patient compliance may also have played a role.

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

The evidence suggested that retinoids were moderately effective as monotherapy at doses of 75 mg/day or 1 mg/kg per day. Acitretin was as effective as etretinate, which was less effective than CSA. The evidence supported the use of combined treatments of a retinoid and PUVA. This combination was more effective than retinoid therapy alone and had the advantage of lowering the cumulative UVA dose.

There was no evidence from RCTs to support the use of methotrexate.

PUVA using oral psoralen (8-methoxypsoralen, 0.6 to 1.0 mg/kg) was found to be effective in clearing psoriasis, and PUVA using topical psoralen ('bath PUVA') was equally effective. UVA alone, however, did not clear psoriasis.
UVB phototherapy was effective in clearing psoriasis. Compared with broadband UVB, narrowband UVB (311 nm) offered the possibility of clearance with fewer episodes of erythema and a lower cumulative dose of UVB. There was no evidence from RCTs comparing narrowband UVB with PUVA. 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 and/or UVB. 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.

Evidence from the one eligible RCT suggested that individual patients may respond to treatment with hydroxyurea.

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.

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

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

Cost information
While several analyses of the costs of psoriasis treatment have been published, none has yet provided a full assessment of the treatment costs.

Authors’ conclusions
The findings showed that there is firm RCT evidence of the effectiveness of some systemic treatments for severe chronic plaque psoriasis. In particular, there was evidence to support the use of CSA, 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, and fumarates.

There was a lack of firm RCT evidence to support the use of other treatments for severe chronic plaque psoriasis, such as methotrexate, hydroxyurea and azathioprine. One RCT showed moderate efficacy for sulphasalazine.

CRD commentary
The research question for this review was fairly broad, but was well defined and explicit in relation to the participants and study designs. The identification of appropriate outcome measures a priori may have strengthened the review.

The search strategy appeared appropriate. The results were cross-checked with the trials databases of specialist groups in the area of dermatology, which was useful. The reference lists of the studies identified by the electronic searches provided additional material, but even so, some literature might have been missed. In particular, no attempts to locate unpublished studies were reported, and there did not appear to have been any contact with other dermatologists or the original authors. The possibility of publication bias was not assessed using, for example, the Begg-Mazumdar test or funnel plot analysis. In a subject area where there are a large number of studies, such an analysis may have been beneficial.

While the trials were considered to be valid if they met the inclusion criteria and supplied sufficient data for further analysis, a more rigorous assessment of the quality of the research base may have strengthened the report. In addition, a more comprehensive description of the process by which the review was conducted would have been useful, in particular the methods used to extract and cross-check the data.
The conclusion drawn and the consequent recommendations appear to follow well from the data presented. The implications for health professionals and the recommendations for future research were comprehensive, and appear to have been written with regard to the limitations of the review as well as the information it found.

Several competing interests were declared. Prof. Griffiths is a consultant to Boots Healthcare International and Novartis Pharma. The Dermatology Centre (Manchester), where three of the authors work, has received grants from Leo Pharmaceuticals, Boots Healthcare International and Novartis Pharma. Prof. Williams received an honorarium from Novartis Pharma for a lecture given in Rome, while Ms. Clark has received funding from Novartis Pharma to support her postgraduate studies.

**Implications of the review for practice and research**

**Practice:** The authors state that, although the availability of RCTs has dictated that the report dealt exclusively with systemic treatments and phototherapies, it is important to be aware that patients with severe psoriasis are frequently treated by means of in-patient 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 in-patient or day-treatment centre management.

**Research:** The authors state that high-quality RCTs are needed in a number of areas, but suggest that two critical steps should be taken before further trials are started. First, outcome measures of relevance to both clinicians and patients should be developed to assess therapeutic response in psoriasis. Second, a definition of ‘severe psoriasis’ should be established. 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 authors state that the following RCTs of treatments for severe psoriasis could be justified: CSA versus methotrexate; systemic therapy or phototherapy versus in-patient and/or day-treatment centre management; acitretin versus methotrexate in a long-term study; fumarates versus methotrexate in both short- and long-term studies; narrowband UVB versus PUVA in both short- and long-term studies; hydroxyurea versus placebo; azathioprine versus placebo; and 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 in-patient 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.

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