A systematic review of five systemic treatments for severe psoriasis

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Authors' objectives
To assess the effectiveness and safety of interventions used with chronic plaque-type psoriasis.

Searching
MEDLINE was searched from 1966 to August 1994 using the following search terms: 'psoriasis', 'methotrexate', 'retinoids', 'cyclosporins', 'PUVA therapy', 'photochemotherapy', 'RePUVA', 'ultraviolet therapy' and 'irradiation'. In addition, 23 experts and 5 pharmaceutical companies were contacted, and 22 abstract books of symposia and congresses and references from retrieved studies were handsearched. Textbooks, reviews, editorials, letters, free or rapid communications, and existing guidelines were also examined. Studies published in English, French, German or Dutch were selected.

Study selection
Study designs of evaluations included in the review
The selection criteria for the study design were unclear. It appears that the analysis was based on a number of uncontrolled case series. Patient series and case reports describing fewer than five patients, or those with inadequate documentation of outcomes or other data, were excluded.

Specific interventions included in the review
Evaluations of ultraviolet B (UVB), photochemotherapy (PUVA), methotrexate, retinoids and cyclosporin (CYA), which are used to promote remission of chronic plaque-type psoriasis, were included. Evaluations of the following were excluded: maintenance treatment; long-term management with interval treatment; antipsoriatic combination therapies; treatments with obsolete or inadequate dosage regimens; home UVB treatment; combined therapy with salt baths and partial UVB irradiation; partial UVA irradiation; filtered sunlight; non-oral application of psoralens, methotrexate, retinoids and CYA; methotrexate doses of more than 25 mg/week; retinoid doses of less than 25 mg/day or 0.5 mg/kg per day; CYA doses of less than 2.5 mg/kg per day or more than 5 mg/kg per day.

Participants included in the review
Severe psoriasis. Studies recruiting adults with chronic plaque-type psoriasis were included. Reports on pustulosis palmoplantaris, generalised pustulosis, psoriasis erythroderma, psoriasis arthropatica, and psoriasis unguium were excluded.

Outcomes assessed in the review
Rates of symptom improvement and the incidence of adverse effects were assessed. Clearance, good, moderate, and poor response to treatment were defined, respectively, as 95 to 100%, greater than 75%, 50 to 75%, and less than 50% improvement of the outcome parameters relative to the baseline. The outcome parameters included the psoriasis area and severity index (PASI), average global scores, and percentages of body surface involved. The adverse effects were classified as mucocutaneous, gastrointestinal, laboratory, and miscellaneous.

How were decisions on the relevance of primary studies made?
All reports were independently screened for inclusion by two reviewers, and any disagreements were resolved by recourse to a third reviewer.

Assessment of study quality
The authors mentioned that they assessed validity, but provided no further details of the validity assessment.

Data extraction
Data were extracted on the following: the year of publication; study design; the number of patients; type, severity and duration of psoriasis; dosage and/or dosing scheme; treatment duration; definition of treatment success; outcome; side-effects; and the number of, and reasons for, drop-outs. For each patient series, the proportion of patients with clearance, good, moderate and poor response to treatment was extracted. In addition, the total number of drop-outs and the number caused by adverse effects were extracted for each series.

Methods of synthesis

How were the studies combined?
The authors appear to have made indirect comparisons across studies. Averages weighted by sample size were calculated across studies for clearance, good, moderate, and poor response to treatment, and drop-outs. Studies only reporting clearance or good response, and not differentiating between moderate and poor response, were used only for calculating the average percentage of patients with good response; they were not included in calculations of moderate and poor response. For each category of adverse effects, the treatment-specific incidence rates were estimated by dividing the frequency of the side-effects by the total treatment duration in weeks.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review

The actual number of studies included was not explicitly stated. The analysis was based on 129 patient series reporting on 13,677 participants.

Data on effectiveness.

PUVA was associated with the highest clearance rate (70%) followed by UVB (44%). PUVA also produced the highest proportion of patients with a good treatment outcome (83%), followed by UVB (68%) and CYA (64%). The retinoids etretinate (ETR) and acitretin (ACI) both showed lower proportions of patients with good treatment results (both 56%). However, ETR produced clearance in more patients than did ACI. No eligible evaluations of methotrexate were identified.

Data on adverse effects and drop-outs.

Of the included patient series, 59% reported adverse effects and 53% reported the numbers of, and reasons for, withdrawal. Most of the adverse effects associated with the use of UVB, PUVA, ETR and ACI were in the mucocutaneous category. Most of the adverse effects associated with CYA were miscellaneous (included cardiovascular adverse effects). The incidence rates per week were highest for ACI and ETR, and lowest for PUVA and UVB. Less than 5% of the drop-outs were related to adverse effects. The overall drop-out rate was highest for UVB, ETR and CYA.

Authors' conclusions

Treatment of sever psoriasis should start with photochemotherapy. However, further research is required in this area.

CRD commentary

The research question, and the selection criteria for the participants, interventions, and outcomes were clearly explained. However, the protocol for selecting studies on the basis of their design was unclear. Good details of the search strategy were provided, but access to additional databases including those representing the grey literature, may have been useful. The validity assessment was mentioned very briefly and more details would have been helpful. Further details of other aspects of the primary studies would also have been useful, particularly those concerning the characteristics of the participants.

The methods used for pooling the data (generating a weighted average across studies) produced summary results with limited reliability given that there were few details of study methodology; the results appear to have come from
uncontrolled case series. These results were then compared indirectly across unrelated studies with possible heterogeneity in terms of the participants, interventions and outcomes. For these reasons, the findings of this review should be treated with a great deal of caution. The authors acknowledged the possibility of selection bias, in that patients are likely to be allocated to receive certain treatments in accordance with the severity of psoriasis.

**Implications of the review for practice and research**
The authors state that the suggestion that treatment of severe psoriasis should start with PUVA should be confirmed with comparative controlled trials using treatment protocols that adhere to currently accepted standards. Great effort should be put into the standardisation of the method used to measure the outcomes, in order to reduce unwanted variability.

**Bibliographic details**

**PubMedID**
9470912

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Chronic Disease; Dermatologic Agents /therapeutic use; Humans; PUVA Therapy; Psoriasis /drug therapy /radiotherapy; Ultraviolet Therapy

**AccessionNumber**
11998000690

**Date bibliographic record published**
30/09/1999

**Date abstract record published**
30/09/1999

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.