Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials


CRD summary
The authors concluded that the effects of approved systemic agents for moderate-to-severe psoriasis differed considerably. Infliximab was the most effective agent. Although the review used appropriate methods to identify and obtain data, the synthesis of data was flawed, so the conclusions about the relative efficacy of agents are not likely to be reliable.

Authors’ objectives
To evaluate the efficacy and tolerability of approved systemic treatments for moderate-to-severe plaque psoriasis.

Searching
Three recently published health technology assessments on systemic treatments for psoriasis were hand-searched for studies published until June 2004. MEDLINE, EMBASE, SCOPUS and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published between June 2004 and December 2007. Search terms were reported. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared the efficacy of recommended therapeutic doses of biological and non-biological systemic treatments approved for moderate-to-severe plaque psoriasis with placebo or another active treatment, were eligible for inclusion. Trials had to have at least 50 patients in Europe or North America and had to assess outcomes using the Psoriasis Area and Severity Index. The review defined moderate-to-severe psoriasis using a Psoriasis Area and Severity Index cut-off of seven. The primary review outcome was the proportion of patients with at least 75% reduction in Psoriasis Area and Severity Index. A number of secondary outcomes were also assessed.

The included trials evaluated ciclosporin (1.25 to 5mg/kg daily included in analyses), etretinate (0.5mg/kg daily), methotrexate (15mg weekly), fumaric acid esters and biologic agents (infliximab 3 or 5mg/kg daily, etanercept 25 to 100mg weekly, efalizumab 1 or 2mg/kg weekly and adalimumab 80mg for week one then 40mg every other week). All included patients were adults and the authors stated that females were under-represented. Some patients had received prior systemic treatment and/or phototherapy. Where used, concurrent topical treatments included steroids and salicylic acid. Most trials were sponsored by manufacturers. The time until assessment of the primary outcome ranged from eight to 16 weeks.

Two reviewers independently selected studies. Disagreements were resolved by consensus among all reviewers.

Assessment of study quality
Two reviewers independently assessed study validity using the Jadad criteria which assessed randomisation, blinding and reporting of withdrawals. Each trial was awarded a score up to a maximum of 5 points. Disagreements were resolved by consensus among all reviewers.

Data extraction
Two reviewers independently extracted data. Where only mean changes and standard deviations in Psoriasis Area and Severity Index were reported, proportions of patients achieving 75% reduction in Psoriasis Area and Severity Index response were estimated assuming a normal response distribution for Psoriasis Area and Severity Index changes. Percentages of patients with 75% reduction response in Psoriasis Area and Severity Index were reported for each treatment group. Disagreements were resolved by consensus among all reviewers.

Methods of synthesis
Trials comparing interventions with placebo were pooled according to drug. Heterogeneity was assessed using the I² and
the χ² statistics. The relative effectiveness of different interventions was then assessed by crudely ranking and comparing the sizes of the pooled risk difference.

For double-blind RCTs, pooled absolute risk differences (RDs) in 75% reduction in Psoriasis Area and Severity Index response rates, with 95% confidence intervals (CI), were calculated for each treatment using a random-effects model. For continuous outcomes, such as mean monthly average of adverse events and withdrawals, the weighted mean difference (WMD) with 95% confidence intervals was calculated; weighting was by sample size. Potential differences in baseline risk among trials were examined by comparing data from control groups. Meta-regression was used to explore the influence of baseline severity, permitted concomitant treatment and study quality.

**Results of the review**

Twenty-four RCTs were included in the review (n=9384 patients). Seventeen trials scored 5 out of 5 on the Jadad scale, two trials scored 4 points, four trials scored 3 points, three trials scored 2 points and two trials scored 1 point.

**Efficacy:** Psoriasis Area and Severity Index 75% reduction response rates for ciclosporin varied considerably (range 28 to 97%).

**Meta-analyses:** Sixteen double-blind RCTs were included in meta-analyses. The authors stated that infliximab (RD 77%, 95% CI 72 to 81; three trials) had significantly higher response rates for 75% reduction in Psoriasis Area and Severity Index than all other treatments. Adalimumab (RD 64%, 95% CI 61 to 68; one trial) had higher response rates than ciclosporin (RD 33%, 95% CI 13 to 52; two trials), efalizumab (RD 24%, 95% CI 19 to 30; five trials), etanercept 50mg twice weekly (RD 44, 95% CI 40 to 48; three trials) and etanercept 25mg twice weekly (RD 30%, 95% CI 25 to 35; three trials). Efalizumab (RD 24%, 95% CI 19 to 30; five trials) had a significantly lower response rate for 75% reduction in Psoriasis Area and Severity Index than fumaric acid esters (RD 48%, 95% CI 32 to 64; one trial).

**Tolerability:** The highest withdrawal rates were for methotrexate (average monthly rate 7.3%) and fumaric acid esters (average monthly rate 10.2%). Compared to placebo, the pooled monthly incidence rate was 2.5% for infusion reactions with infliximab and 4.8% for injection site reactions with etanercept. The monthly incidence rate was 1.8% higher for upper respiratory tract infections with adalimumab compared to placebo.

**Authors' conclusions**

The efficacy of approved systemic agents for moderate-to-severe psoriasis differed considerably. Infliximab was the most effective.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched and no language restrictions were applied, but no attempts were made to minimise publication or language bias. Appropriate methods were used to minimise reviewer error and bias during the review process. Only RCTs were included, validity was assessed but only aggregated scores were reported. It appeared that the decision to pool only double-blind RCTs was taken post-hoc, but a priori analysis are preferred as a method of reducing potential bias. Double-blind placebo RCTs were combined using meta-analysis and heterogeneity as assessed for trials evaluating the same agent. The authors’ conclusions about relative efficacy were based on informal indirect comparisons; it was unclear how the statistical significance of differences between different agents was tested. Adjusted indirect comparison methods were not used, which suggested that the findings were subject to bias and may not be reliable. In addition, indirect comparisons are only likely to be reliable if studies are comparable in terms of design and population. Although the review used appropriate methods to identify and obtain data, the synthesis of data was flawed, so the conclusions are not likely to be reliable.

Three of the authors have been investigators or consultants for various pharmaceutical companies; they stated that this work was not directly related to this review.

**Implications of the review for practice and research**
Practice: The authors stated that ‘published evidence questions regulatory guidelines that recommend biologics as second-line therapy for moderate-to-severe plaque psoriasis’.

Research: The authors stated that studies are required to evaluate the cost-effectiveness of biological interventions such as infliximab and adalimumab. They also stated that there is a need for pragmatic RCTs that last at least two years to directly compare different biological agents with each other and with conventional systemic psoriasis treatments. The comparative efficacy of different biological agents should also be evaluated in the sub-group of patients who have failed to respond to conventional systemic treatments.

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