Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: a meta-analysis

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CRD summary
This review found that ustekinumab was a safe and effective treatment for psoriasis in adult patients. Despite some limitations in the review and in the evidence base, the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy and safety of ustekinumab (immunoglobulin monoclonal antibody drug) in patients with psoriasis.

Searching
MEDLINE, EMBASE, CNKI, VIP and Wanfang databases were searched up to 2009 for relevant studies; search terms were reported. References of primary studies in some academic journals (unspecified) were searched.

Study selection
Randomised controlled trials (RCTs) that compared ustekinumab with placebo in patients (18 years and over) psoriasis were eligible for inclusion. Eligible patients had baseline scores on the Psoriasis Area and Severity Index (PASI) of 12 points or more, with at least 10% of body surface area involved. Patients with non-plaque type psoriasis were excluded.

The primary outcome was the proportion of patients who achieved 75% or more improvement in PASI score (PASI-75) at weeks 12 and 28 of follow-up. Secondary outcomes were results from the physician's global assessment, changes on the Dermatology Life Quality Index (DLQI), and adverse events.

The included trials were conducted in the USA and Europe from 2007 to 2008. The age range of participants was 44 to 47 years. The proportions of men ranged from 59 to 73%. Psoriasis duration ranged from 16.9 years to 20.4 years. The body surface area of psoriasis ranged from 25.2% to 28.5%; baseline PASI scores ranged from 18.8 to 20.5. Across the trials, 19 to 36.7% of patients presented with psoriatic arthritis.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed using the Cochrane Collaboration guidelines for the baseline characteristics of the RCTs including allocation concealment, blinding and follow-up.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data to calculate risk ratios (RR) for dichotomous outcomes, mean differences (MD) for continuous outcomes, with 95% confidence intervals (CI) for the estimates.

Methods of synthesis
Pooled risk ratios, weighted mean differences (WMD) or standardised mean differences (SMD), with 95% confidence intervals for the summary estimates, were calculated using a fixed-effect model. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. In the event of statistically significant heterogeneity, the results were combined using a random-effects model.

Subgroup analyses were conducted to explore some clinical differences in dose groups.

Results of the review
Three RCTs (2,316 patients) were included in the review. Stratified randomisation, blinding and the use of intention-to-treat analyses were reported in all the trials. Follow-up was described and ranged from 17.9 to 19.7 weeks. None of the
trials reported methods used for allocation concealment. All three trials compared ustekinumab doses of 45mg and 90mg with placebo.

**Ustekinumab 45mg versus placebo**: Statistically significant benefits were observed with doses of 45mg ustekinumab for the proportion of patients attaining PASI-75 (Psoriasis Area and Severity Index score of 75%) at 12 weeks (RR 19.90, 95% CI 13.38 to 29.60), the Physician's Global Assessment at 12 weeks (RR 72.19, 95% CI 17.04 to 290.42), scores on the DLQI (Dermatology Life Quality Index; RR 12.73, 95% CI 8.86 to 18.30). There was no statistically significant heterogeneity found across the trials for these outcomes. There were no statistically significant differences in PASI scores at 12 weeks, but there was substantial heterogeneity identified across the trials for this outcome ($I^2=100\%$).

**Ustekinumab 90mg versus placebo**: There were statistically significant benefits at 12 weeks observed for the higher dose of ustekinumab compared with placebo for the proportion of patients achieving PASI-75 (RR 21.56, 95% CI 14.51 to 32.04), the Physician's Global Assessment (RR 85.97, 95% CI 21.36 to 345.97) and DLQI (RR 13.07, 95% CI 9.09 to 18.79). There was no statistically significant heterogeneity observed across these outcomes. There were no differences observed between placebo and this dose of ustekinumab for PASI score, but substantial heterogeneity was identified across the trials ($I^2=100\%$).

**Ustekinumab 45mg versus ustekinumab 90mg**: There were statistically significant benefits observed in the group treated with 90mg ustekinumab compared with those treated with 45mg ustekinumab for the proportion of patients who achieved PASI-75 at 12 weeks (RR 0.92, 95% CI 0.86 to 0.99), although no significant differences were observed at 28 weeks (two trials). There was no statistically significant heterogeneity observed for these outcomes. There were no significant differences between dose groups in the Physician's Global Assessment at 12 weeks, but benefits favouring the 90mg ustekinumab group were observed at 28 weeks (RR 0.69, 95% CI 0.58 to 0.82). There were no significant differences between the groups in change in PASI scores and DLQI scores at 12 weeks and 28 weeks.

There were no differences observed between the 45mg and 90mg doses of ustekinumab and each dose compared with placebo for any mild-moderate or serious adverse events. No statistically significant heterogeneity was observed across the trials for these outcomes.

**Authors' conclusions**

Ustekinumab was a safe and effective treatment for psoriasis in adult patients, but further research was required to clarify the safety profile of this treatment, particularly at higher doses over longer treatment periods.

**CRD commentary**

The review addressed a clearly defined question. Criteria for the inclusion of studies in the review were stipulated. Appropriate databases were searched for relevant studies, but lack of specificity on search dates and journals that were handsearched meant that the search could not be easily reproducible. There were no attempts to identify unpublished studies, which meant that there was a possibility of publication bias. It was unclear if language restrictions were imposed on the search, so there was some potential for language bias. The reviewers reported steps to minimise errors and biases (duplicate, independent processes) for data extraction, but not for the selection of studies or the assessment of methodological quality.

The decision to combine the results of the review in a meta-analysis appeared to be justified because of clinical similarities among the groups of included patients and statistical homogeneity in some results. The authors acknowledged some of the limitations of the review, such as the small numbers of included trials, the lack of reported allocation concealment in the trials, the heterogeneity of some outcomes examined, and the potential lack of generalisability of the findings to other populations outside of the USA and Europe.

Despite the limitations in the review and the evidence base, the large treatment effects observed suggest that the authors' conclusions are likely to be reliable.

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

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that future research should determine the efficacy and safety of ustekinumab at higher doses over longer durations of follow-up to determine the optimal dose of ustekinumab.
Funding
Lanzhou University, Gansu, China.

Bibliographic details

PubMedID
20923370

DOI
10.3109/09546634.2010.487890

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal /adverse effects /therapeutic use; Antibodies, Monoclonal, Humanized; China; Dose-Response Relationship, Drug; Drug Administration Schedule; Female; Follow-Up Studies; Humans; Interleukin-12 /immunology /therapeutic use; Interleukin-23 /immunology /therapeutic use; Male; Psoriasis /diagnosis /drug therapy; Randomized Controlled Trials as Topic; Risk Assessment; Severity of Illness Index; Treatment Outcome; Ustekinumab

AccessionNumber
12011007326

Date bibliographic record published
29/02/2012

Date abstract record published
18/08/2012

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.