Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that, compared with placebo, anti-interleukin 12 and 23 or anti-tumour necrosis factor alpha treatment did not significantly affect the rate of major adverse cardiovascular events in patients with chronic plaque psoriasis, but the trials might have been underpowered to detect significant differences. This was a well-conducted review and the authors’ conclusions reflect the evidence and seem appropriate.

Authors’ objectives
To assess the effects of biologic therapies for chronic plaque psoriasis, in terms of major adverse cardiovascular events (MACEs).

Searching
MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were searched for articles from inception to May 2011, without language or publication status restrictions. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared monotherapy with anti-interleukin 12 and 23 agents (ustekinumab or briakinumab), or anti-tumour necrosis factor alpha (anti-TNFalpha) agents (adalimumab, etanercept, or infliximab) versus placebo, for the treatment of adults with chronic plaque psoriasis, were eligible for inclusion. Eligible trials were required to be double blind and to report MACEs (composite measure of myocardial infarction, cerebrovascular accident, or cardiovascular death). Trials of psoriatic arthritis and palmo-plantar psoriasis were excluded.

The duration of the included RCTs ranged from 10 to 24 weeks. Where reported, the mean age of patients ranged from 42.1 to 46.2 years, and the mean duration of plaque psoriasis ranged from 13.9 to 21.5 years. At baseline, the mean percentage of affected body surface area, where reported, ranged from 22.3 to 46.2. Where reported, the mean baseline Psoriasis Area and Severity Index score (measuring the grade of erythema, induration, scaling of plaques, and the body surface area affected) ranged from 17.5 to 28.38 (a score of zero indicated clear body surface area and a score of 72 indicated maximum severity).

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Six reviewers assessed trial quality based on adequacy of randomisation, allocation concealment, and blinding. Disagreements were resolved by consensus.

Data extraction
Six reviewers extracted the number of MACEs in patients receiving at least one dose of the intervention or placebo. Disagreements were resolved by consensus.

Methods of synthesis
All doses of each agent were combined and the pooled risk differences in events per person-year, with 95% confidence intervals, were calculated using a fixed-effect model. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$.

Subgroup analyses were undertaken by agent. Sensitivity analysis was performed, excluding three trials exclusively of Asian patients. Publication bias was assessed through visual inspection of funnel plots.

Results of the review
Twenty-two RCTs (10,183 patients) were included in the review; 7,037 patients received an intervention and 3,146 received placebo. All trials were adequately randomised and all were double blind. Fourteen RCTs (64%) reported
adequate allocation concealment.

For the overall analysis, there were no statistically significant differences in major adverse cardiovascular events (MACEs) between patients given placebo and those treated with an anti-interleukin 12 and 23 (RD 0.012 events per person-year, 95% CI -0.001 to 0.026; nine RCTs), or with an anti-TNFalpha (RD -0.0005 events per person-year, 95% CI -0.010 to 0.009; 15 RCTs). Subgroup analyses by agent showed similar results. The sensitivity analyses did not significantly alter the results. There was no evidence of statistical heterogeneity for any comparison ($I^2$ was zero).

There was no evidence of publication bias.

**Authors’ conclusions**

Compared with placebo, an anti-interleukin 12 and 23 or an anti-TNFalpha treatment did not significantly affect the rate of major adverse cardiovascular events in patients with chronic plaque psoriasis. The evidence highlighted the limitations of the RCTs in reliably interpreting the significance of rare events, as the trials were often underpowered and too short to detect rare or long-term adverse events.

**CRD commentary**

The review question was clear and was supported by clearly defined inclusion criteria. A satisfactory literature search was undertaken and steps were taken to reduce the potential for language and publication bias. Publication bias was formally assessed and no evidence was found. The authors acknowledged that the reliability of their findings might have been reduced due to many of the trials reporting no events. Each stage of the review process was performed in duplicate, thereby reducing the potential for reviewer error and bias.

Quality assessment of the trials suggested generally high quality, but withdrawals and intention-to-treat analysis were not assessed. There was no evidence of statistical heterogeneity and the analyses seem to have been appropriate. It was unclear if combining all doses of each agent affected the results, and there were approximately twice as many patients in the intervention group compared with the placebo group.

This was a well-conducted review and the authors’ conclusions reflect the evidence and seem appropriate.

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

**Practice:** The authors reported that the briakinumab trials had been discontinued pending investigations into possible links with MACEs and, until more definitive data become available, extreme vigilance for cardiovascular risk should be exercised when initiating anti-interleukin 12 and 23 agents in patients with psoriasis. The authors suggested that the limitations of RCTs in reliably detecting the significance of rare events should be considered for the benefit of the patients in these trials and those treated once the drugs are approved.

**Research:** The authors did not state any implications for research.

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