Letter

Response to commentary by Dixon and Silman on the systematic review and meta-analysis by Bongartz *et al*.

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See related commentary by Dixon and Silman, http://arthritis-research.com/content/8/5/111

Dixon and Silman [1] provide an insightful review of the methodology and results of our meta-analysis of harmful events among patients with rheumatoid arthritis treated with anti-tumour necrosis factor (TNF) antibody agents [2].

Meta-analyses of valid randomized trials of like agents ensure that, in the absence of a treatment effect, patients with rheumatoid arthritis in the intervention and placebo groups should share the same risk for developing serious infections or malignancy. Etanercept, although it needs study, was not included in our analysis because it is dissimilar from the anti-TNF agents.

A particular advantage of such trials is that there is almost complete follow up of each treatment arm, with patients maintained in the assigned groups for intent-to-treat analysis at least for the randomized portion of the trial, even if drug exposure is discontinued for whatever reason. The appropriate statistical analysis of such comparator groups in the trial context of equivalent follow up in each arm is an odds ratio rather than incidence rate ratio. Dixon and Silman raise the possibility of bias in our analysis because of the greater dropout rate in the placebo arm, potentially leading to a lower detection threshold for malignancies in the placebo compared with the treatment arm. We found no evidence for a difference in detection thresholds in the placebo follow-up period, which was equivalent to the treatment arm in duration for the controlled phase of the studies on which we performed the analysis. Dixon and Silman also note a classification or detection bias for serious infections because of the greater likelihood of placebo patients being hospitalized. In this case our analysis would underestimate the true risk for serious infection in treated compared with control patients.

In practice, lack of efficacy with the standard dose of 3 mg/kg of infliximab results in many patients using higher doses; as many as 61% of patients with rheumatoid arthritis after 1 year of use receive, on average, 4.9 mg/kg of infliximab [3]. The manufacturer's product label for infliximab allows doses up to 10 mg/kg of infliximab for partial responders [4]. Thus, not only are our findings applicable to clinical practice and biologically plausible, but they also fulfill the dose-effect criterion for causality.

The low risk in the comparison group may be real, the result of chance, or due to an as yet unclear systematic design or analysis flaw of all included randomized controlled trials. We are wary of the interpretation of lower risk being due to chance or some other drug effect, which may give a false sense of security about the drug in question [5].

Long-term observation of large, unselected case cohorts, using methods such as treatment registries will provide widely generalizable information about the treatment response. However, it is even more difficult to compose the appropriate comparator group and control for all potential confounding factors in a registry than in a well conducted randomized clinical trial. Early conduct of meta-analyses with methods, such as those we put forward, to estimate the rate of rare events [2] can yield data that manufacturers and regulatory bodies, and patients and clinicians should consider when making policy and clinical decisions, respectively.

Competing interests

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References

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