Commentary

# Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz *et al*.

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## Abstract

A recent meta-analysis of randomized clinical trials reported by Bongartz and coworkers raised concerns about an increased rate of malignancy and serious infection in rheumatoid arthritis patients treated with anti-tumour necrosis factor monoclonal antibodies. This commentary discusses some of the methodological issues in their analysis and urges caution in interpreting the results.

## Introduction

The introduction of anti-tumour necrosis factor (TNF) agents and their widespread use, particularly for treating rheumatoid arthritis (RA), is based on favourable results from large-scale randomized clinical trials (RCTs). The trial data were rightly also utilized to investigate possible hazards associated with the use of these drugs, and the results have mostly been reassuring. The problem is that all of these trials are individually too small and of insufficient duration to provide useful data on rare but serious long-term hazards. In addition, RCTs are typically conducted in lower risk patients (i.e. those patients with significant current or recent co-morbidity are excluded).

One approach to overcome the small size of individual studies is to undertake a pooled or meta-analysis of all relevant trials. Although this is indeed a frequently used approach to derive robust estimates of efficacy, the data gathered in trials on potential long-term hazards are not routinely subjected to similar pooled analysis. In an attempt to overcome the small number problem to examine serious hazards from using RCT data, Bongartz and coworkers [1] conducted a meta-analysis of the incidence of infections and cancer occurring in the different treatment arms of the published anti-TNF monoclonal antibody trials.

## Summary of methods and findings

The meta-analysis identified nine trials of the use of infliximab or adalimumab in RA. The authors did not include trials of etanercept because they argue that the biological activity of this receptor fusion protein is too different from that of the monoclonal antibodies, specifically with regard to the relationship to infection and tumour growth. The means of ascertainment of serious adverse events were not identical to those used in the original published trials, because the authors took additional steps both to verify the nature of the events and to include events that occurred during the – presumed open label – period of follow up. They did not attempt to calculate incidence rates (e.g. per 1000 person-years of exposure), given the difficulty in ascertaining the exposure periods; however, they calculated odds ratios (ORs), assuming equality of follow up between the participants randomized to the different arms within each of the individual trials.

Their results suggest a threefold (OR 3.3, 95% confidence interval [CI] 1.2-9.1) increased risk for malignancy in anti-TNF-treated patients compared with those in the standard treatment arms of the included trials. This risk was concentrated in those on high-dose therapy defined as ≥6 mg/kg infliximab over 8 weeks or (assumed but unclear in the report) ≥40 mg adalimumab every other week, who had an OR of 4.3 (95% CI 1.6-11.8). There was no important increased risk below these levels. Many malignancies in the anti-TNF arms of the trials were nonmelanoma skin cancers (9/35), and a further four were identified within 6 weeks of starting therapy. Even excluding these cases, the increased risk compared with the comparison arms was still present, especially because there was only such one cancer in the comparison arms. The risk for serious infections was also raised but to a more modest extent. Thus, there was an

CI = confidence interval; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized clinical trial; TNF = tumour necrosis factor.

overall increase of twofold (OR 2.0, 95% CI 1.3-3.1) but with a much less marked influence of dose. Therefore, these data overall raise concerns about the safety of anti-TNF monoclonal antibody therapy in RA, especially when used at high doses.

## Commentary

However, there are a number of areas in which caution is required. First, the external validity of the findings to current therapeutic practice should be considered. As stated above, they did not include etanercept, which, for example, is the most popular used anti-TNF agent in the UK. Indeed, as the authors argue based on biological principles, this agent may not be expected to carry the same risk. Second, the dose of infliximab in standard RA regimens is typically 3 mg/kg; in the trials evaluated there was only one malignancy (a lymphoma) in a patient treated with this dose of infliximab.

Third, and of greater concern, is the malignancy rate in the control arms, which was unexpectedly low. Among 1512 comparison arm patients, followed for what would appear to be an average of 34 weeks, there was only one malignancy, excluding the two basal cell carcinomas. In a typical RA population, or indeed a general population sample of this age group, one might expect an incidence of around 8/1000 per year, which is at least eight times that seen in the comparison arm patients and is of the same order of magnitude as that seen in the anti-TNF arms of the trials. Does the threefold increased risk reflect an unexpectedly low rate of cancer in the placebo arms rather than a genuine increased risk from anti-TNF therapy? It is not clear why the rate should have been so low. If low-risk patient selection were a factor, then this should have operated equally in the anti-TNF group. There is, however, a possible explanation based on the differential dropout between the studies following entry into the trials. Typically, all patients entered into these explanatory RCTs are, to varying extents, screened to exclude pre-existing malignancy, for example with chest radiography. Thus, in such patients there is a 'telescoping' of ascertainment of malignancy before study entry, with the consequence that fewer new malignancies will be identified in the early post-trial entry period. As the authors acknowledge, in their meta-analysis four out of the nine trials had a higher dropout in the placebo arms, meaning that more patients withdrew from follow up sooner. Given the reduced risk (as outlined above) during the early follow-up periods, this would lead to a bias toward detection of malignancy in the anti-TNF arms during the later periods of follow up. Although all malignancies could have been captured by the US Food and Drug Administration beyond the end of the trial, it is less likely that the placebo arm patients will have their malignancies spontaneously reported once they enter the unblinded phase.

Of the 26 malignancies in the anti-TNF arms, 10 were lymphomas. The possibility that such therapy might increase lymphoma risk was raised previously [2], although it has been difficult to disentangle the risk from the therapy from the increased risk in patients with severe RA [3,4]. Indeed, it has been argued that by reducing inflammatory activity, anti-TNF agents might have the ability to reduce lymphoma risk [5]. It is perhaps also surprising there were no lymphomas in the comparison patients, given the previously reported increased risk, especially in those with severe disease treated conventionally [6]. However, using randomized trials, the confounding effect of severity should have been allowed for, and so these data do raise concerns about an increased risk for this tumour that will require longer term follow up of much larger cohorts.

The risk for infection was less marked than that for malignancy in the analysis. Serious infections after randomization might be assumed to be solely due to a drug effect. However, serious infection is based on hospitalization or intravenous antibiotic use, and the threshold for these interventions might differ both between trials and between treatment arms within a trial; if an individual has a good response to the drug, then there may be a lower threshold for admission to hospital with infection. Thus, in comparison with malignancy, it is much harder to standardize the recording of infections across the different trials. There were 35 serious infections/1000 treated anti-TNF patients, which equates to around 52/1000 person-years (or less, allowing for loss to follow up). It is reassuring in terms of external validity that this rate is broadly similar to those reported by two recent national register studies from Germany (infliximab rate 62/1000 person-years) [7] and the UK (infliximab 55/1000 person-years, adalimumab 52/1000 person-years) [8].

## Conclusion

Individual clinical trials are clearly too small, too selected in the populations studied, and of too short a duration to generate robust estimates of any possible increased risk for rare adverse events. A meta-analysis, such as that conducted by Bongartz and coworkers [1], has the ability to overcome some of these issues and has raised the concern of a potentially serious increased risk for malignancy. However, the interpretation of the results needs to take into account the unexpected and unexplained low risk in the comparison arms. Further answers to these key questions of drug safety will have to await the data rapidly accruing from large national registers of unselected anti-TNF treated patients with the appropriate comparison groups.

## Competing interests

WD is the Clinical Research Fellow and AS is joint principle investigator (with Professor Deborah Symmons) of the British Society for Rheumatology Biologics Register (BSRBR). The goals of the BSRBR are primarily related to examining the long-term safety of biologic agents used in rheumatology. The BSRBR is funded by a grant to the University of Manchester from the BSR, which in turn receives funding from the manufacturers of the agents licensed for use in the UK. The

principal investigators have the normal academic freedoms to exploit and publish the data accruing from the BSRBR, with the approval of the BSR.

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