Observational Studies of Infections in Rheumatoid Arthritis: A Metaanalysis of Tumor Necrosis Factor Antagonists

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ABSTRACT. ***Objective.*** Published metaanalyses of tumor necrosis factor (TNF) antagonists and infection have focused on randomized controlled trials, which tend to have short duration, relatively small size, and stringent inclusion/exclusion criteria that may limit enrollment to patients at low risk of infection. We performed a systematic review and synthesis of observational studies of TNF antagonists and infection risk.

Methods. We conducted a systematic literature search of studies estimating overall risk of serious infection after anti-TNF exposure in rheumatoid arthritis (RA). We estimated a pooled relative risk (RR) for the relevant observational studies, using a random-effects model.

Results. Five cohort studies and 2 nested case-control studies were included in the metaanalysis. Anti-TNF therapy appeared to significantly increase risk of serious infection (pooled adjusted RR 1.37, 95% CI 1.18, 1.60).

Conclusion. Our metaanalysis of observational data demonstrated an increased risk of serious infection in subjects with RA receiving anti-TNF therapy, versus those not receiving these agents. (J Rheumatol First Release April 1 2010; doi:10.3899/jrheum.091107)

Key Indexing Terms:
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METAANALYSIS DISEASE-MODIFYING ANTIRHEUMATIC DRUGS
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Rheumatoid arthritis (RA) is a potentially disabling disease characterized by an overactive immune system and joint inflammation. Current guidelines endorse aggressive treatment with traditional disease-modifying agents (DMARD) and/or newer biologic therapies, notably tumor necrosis factor (TNF) antagonists. Although TNF antagonists are a major breakthrough for patients failing traditional DMARD, safety concerns have emerged, particularly regarding infections. Available data come from both short-term randomized controlled trials (RCT) and longterm observational studies.

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To date, published metaanalyses of TNF antagonists and infection have focused on RCT, which tend to have short duration, relatively small size, and stringent inclusion/exclusion criteria (potentially limiting enrollment to patients at low infection risk). Observational studies may be more generalizable; hence the rationale for our study.

MATERIALS AND METHODS

We conducted a systematic literature search to identify observational studies of TNF antagonists and serious infections in RA. For our metaanalysis, inclusion criteria were an observational study design in RA, providing adjusted relative risk (RR) estimates for overall serious infection with anti-TNF exposures. The definition for serious infection was based primarily on need for hospitalization, but was not otherwise specified (i.e., could include mortality or disability).

We used the text-based computerized search and retrieval system of the US National Center for Biotechnology Information, which accesses over 18 million citations from Medline as well as other life science journal citations. Our search strategy used the terms rheumatoid arthritis, infection, risk, tumor necrosis factor (or TNF or biologic), excluding case reports and clinical trials. We also searched abstracts presented 2002-2008 at annual meetings of the American College of Rheumatology and the European League Against Rheumatism. A review of references from primary and review articles was performed to identify additional studies. One reviewer screened all citations (titles/abstracts); those of relevance were subsequently reviewed in full text to identify the final set of studies.

For the final set of studies, we assessed the quality of each (population sampled, outcome definition, analytical approach), and constructed study summaries and a funnel plot of RR versus precision (precision being the inverse of the RR standard errors).

Our metaanalysis computed a summary RR with 95% CI using a random-effects model. This represented a weighted mean of the adjusted RR from the studies; weights were the inverse of total variance (the sum of between-studies and within-study variances)[1]. We assessed the consistency of treatment effect across studies using Cochran's Q test for heterogeneity[2].

RESULTS

Our electronic search produced 230 citations. Excluding guidelines, commentaries, and studies limited to a single type of infection or on an unrelated topic, we were left with 15 observational studies published as full papers and 2 as abstracts only. The 2 abstracts were excluded, 1 because it included all infections, not just serious infections, and the other because it did not provide adequate summary information about adjusted RR. Of the 15 articles, 1 was excluded because it studied polyarthritis other than RA, and 5 were excluded because they did not provide adjusted RR. Also, in 2 cases, multiple reports came from the same study base. First, Dixon, *et al* produced 2 cohort studies on the same registry population; since more sophisticated methods and updated data were used in the more recent study, that one was included in our metaanalysis[3]. Second, Curtis, *et al* produced 2 reports within the same year[4], but the later report was a secondary analysis, so only the first report was included.

We thus included 5 cohort[1,3,5-7] and 2 nested case-control[8,9] studies (Table 1). One study presented RR estimates separately for the agents infliximab and etanercept[6]; here, we included a single weighted average in our metaanalysis. All studies (Table 1) were of large size with appropriate design and methodology (e.g., uniform outcome ascertainment). Methods used to control for confounding by indication (i.e., RA disease activity) varied, but all included some adjustment for demographics, disease duration, and other drug exposures, including the important potential confounder of corticosteroid use (potentially correlated with both other medication use and infection risk). A plot of RR versus precision suggested a symmetric, inverted funnel shape, implying no publication bias (Figure 1).

The Q test of heterogeneity for the RR was nonsignificant; however, we felt the random-effects model was still appropriate, since the test has limited power, and the estimate of variance between studies suggested by our methods[1] was not null. The summary RR suggested about a 40% increased risk of serious infections in patients with RA exposed to TNF antagonists (RR 1.37, 95% CI 1.18, 1.60). Sensitivity analyses, stratifying by whether the studies used administrative data versus patient registries, showed very similar results for administrative data (RR 1.36, 95% CI 1.02, 1.82) compared to patient registries (RR 1.41, 95% CI 1.17, 1.71).

DISCUSSION

To date, metaanalyses of infection incidence with TNF

Table 1. Studies of tumor necrosis factor (TNF) antagonists and serious infections in rheumatoid arthritis (RA). Adjustments also controlled for RA duration, demographics, and other drugs including corticosteroids. Adjusted RR means serious infections (95% CI).

Study	Year	Design	Country	Sample	Outcome	Comparator	N (Average Followup, yrs)	Adjustments for Differential Prescription/RA Severity	Adjusted RR*
Smitten[8]	2008	Nested case-control	UK	Administrative data	Hospitalization records	No biologic or DMARD	24,530 (2.2)	Rheumatology visits, procedures, NSAID/coxib	1.21 (1.02–1.43)
Schneeweiss[5]	2007	Cohort	USA	Administrative data	Bacterial infection in hospital records	MTX	15,597 (0.4)	Propensity scores (procedures, labs, physician visits)	1.0 (0.6–1.7)
Dixon[3]	2007	Cohort	UK	Patient registry	Self-reported hospitalization, IV antibiotics, or death	Any DMARD	10,829 (1.5)	Baseline RA activity, extraarticular RA features	1.22 (0.88–1.69)
Curtis[4]	2007	Cohort	USA	Administrative data	Infection based on hospital records	MTX	5326 (1.6)	No. of physician visits, disability	1.9 (1.3–2.8)
Bernatsky[9]	2007	Nested case-control	Canada	Administrative data	Infection based on hospital records	No biologic or DMARD	21,670 (6.3)	Extraarticular RA features, visits to rheumatologist	1.9 (0.7–5.3)
Askling[7]	2007	Cohort	Sweden	Patient registry	Infection based on hospital records	Any DMARD	44,946 (–)**	Joint replacement baseline activity, RA hospitalization	1.43 (1.18–1.73)**
Listing[6]	2005	Cohort	Germany	Patient registry	Hospitalization, disability, or death*	Any DMARD	1459 (3.3)	Propensity scores (RA activity, labs, DMARD failure, disability)	2.1 (0.8–5.5) Infliximab 2.2 (0.9–5.4) etanercept

DMARD: disease-modifying anti-rheumatic disease agent. NSAID: nonsteroidal antiinflammatory drug; MTX: methotrexate; coxib: cox-2 inhibitors. * Corresponds to serious infection definition of the International Conference on Harmonization. ** First year of anti-TNF therapy only.

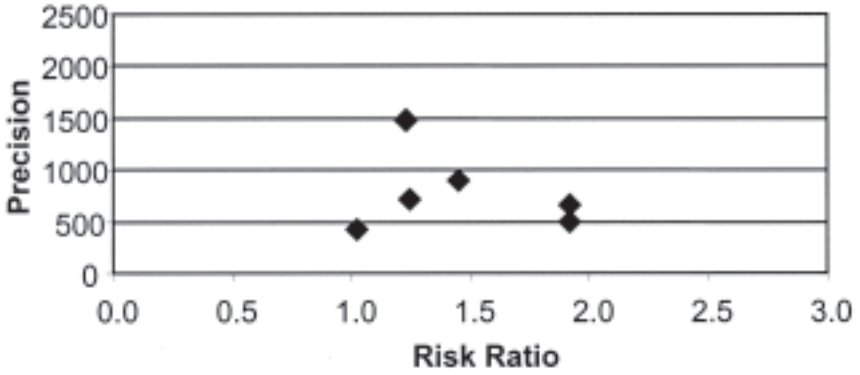

Figure 1. Funnel plot of observational studies of serious infection risk after tumor necrosis factor (TNF) antagonist exposure. Does not include study by Listing, *et al*[6], which produced RR estimates separately for different TNF antagonists. Precision: the inverse of the RR standard error.

antagonists have focused on RCT data. One RCT meta-analysis stressed that increased infection was seen only when the dose exceeded current recommendations[10]. Another RCT metaanalysis demonstrated a pooled OR for serious infection of 2.0 (95% CI 1.3–3.1)[11]; however, this generated considerable debate regarding methodological limitations, including the absence of data on etanercept (one of the most widely used anti-TNF agents) or adjustment for exposure duration, and that induction doses of infliximab were excessive in some cases. The metaanalysis of Alonso-Ruiz, *et al*[12] estimated the RR for serious infections with anti-TNF therapy at 1.4 (95% CI 0.8–2.2). This was interpreted as "no significant combined increases in risk," although the point estimate and the upper limit of the interval obviously do not preclude a real increased risk.

Although our metaanalysis has limitations, we believe they are not greater than those of all recent syntheses (which, to date, have been restricted to RCT data). In all cases, the relevant studies are relatively few. In addition, observational research may include unmeasured confounders. The most troublesome of these, in our case, is RA disease activity. In well done registry studies, carefully collected data on disease activity is believed to be a great advantage over administrative database studies, where attempts to control for disease activity, including propensity scores, are laudable but not ideal. We note, however, that our results seemed relatively consistent across the 2 types of studies. Although most of the recent literature on serious infections in RA has based the outcome definition on requirement for hospitalization, this definition may underestimate the risk for infections that are serious but that do not necessarily require hospitalization; tuberculosis may be a case in point. Hence, the estimate produced in this meta-analysis might be considered conservative.

In metaanalyses, one must always consider the potential of publication bias. Specifically, research results showing an effect are more widely disseminated, and therefore easier to retrieve, than those showing no effect. A plot of the RR and precision estimates for the studies included in our meta-analysis did suggest a symmetric, inverted funnel shape, generally interpreted as implying no publication bias.

There has been great interest recently regarding the timing of infection risk following exposure to TNF antagonists. There are at least 3 studies that highlight high risk in early followup. In the study by Askling, *et al*[7], the risk of infection after TNF antagonist exposure was 1.4 (95% CI 1.2, 1.7) in the first year, 1.2 (95% CI 0.9, 1.5) in the second year, and 0.8 (95% CI 0.6–1.1) thereafter. Dixon, *et al*[3], in subanalyses, found that the relative risk for serious infections was 4.6 (95% CI 1.8, 11.9) during the first 90 days of treatment, and Curtis, *et al* found that any increased risk of serious infections with TNF antagonists was highest in the first 6 months of treatment, and then waned[13]. This phenomenon may represent a depletion of susceptibles, that is, those subjects who are likely to succumb to a serious infection will do so early on, so that RR will be highest in the early phase. Lower disease activity and less glucocorticoid exposure may also result in a real risk decrease over time. Unfortunately, we had inadequate summary data to assess for this phenomenon across studies. Regardless, one would expect if anything that we would be able to show an even higher summary RR, if we had been able to focus on early exposures (e.g., in the first 6 months) across studies.

Some data also suggest that infliximab may heighten infection risk in a more potent way than etanercept. In work by Curtis, *et al*[13], infliximab was more strongly associated with serious bacterial infections in the first 6 months of treatment (RR 2.4, 95% CI 1.2–4.7) than etanercept (RR 1.6, 95% CI 0.8–3.8). However, the only registry publication examining the drugs separately contradicts this[6].

A real advantage of our metaanalysis is that the subjects included are likely more reflective of the overall population with RA, compared to RCT data. Still, some of the results may reflect differential prescription, such that patients receiving TNF antagonists tend to have more severe RA, which itself may be a factor driving increased infection

risk[14]. Also, our findings must be regarded in light of data emphasizing the very high infection risk conferred by corticosteroids[8]. The steroid-sparing effects of TNF antagonists may thus be important to consider when weighing the risks and benefits of biologic therapies for patients not responding to traditional DMARD.

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