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Drug-specific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor α antagonists

In a previous study by our group (1), we observed a significantly increased risk of being hospitalized with a serious bacterial infection among patients with rheumatoid arthritis (RA) who were treated with tumor necrosis factor α (TNFα) antagonists compared with patients with RA who received methotrexate (MTX). Although we showed that this risk was increased during the entire study period (median duration of followup 17 months), the risk was highest within the first 6 months after beginning treatment with the TNFα antagonist. Given our further interest in characterizing drug-specific risks, we evaluated the comparative effects of antibody-based and non–antibody-based TNFα antagonists on the risk of being hospitalized with a bacterial infection.

Extending our previously published analysis (1), we defined cohorts of patients with RA who had at least 2 International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for RA (714.x, excluding 714.3) and were receiving either infliximab or adalimumab, etanercept, or MTX without a TNFα antagonist. Because the number of patients receiving adalimumab (n = 118) was insufficient to permit meaningful conclusions, these patients were excluded from this analysis. All patients exposed to TNFα antagonist were new users, defined as having at least 6 months of nonexposure to these drugs prior to the first filled prescription. Patients were considered at risk of infection within 90 days of the most recent filled prescription for the drug of interest. Patients who were exposed to multiple TNFα antagonists during the same window of risk were excluded.

In a sensitivity analysis, shorter risk windows were used (i.e., 30 days for etanercept and MTX, and 60 days for infliximab). Given our previously observed increased risks within the first 6 months of starting a biologic agent, we separately considered exposure time within and beyond 6 months. Using methods previously described (1), serious bacterial infections were initially identified through administrative claims data. Following nationwide medical record abstraction of hospital records, infections were confirmed independently by infectious disease physicians who were blinded to the medication lists for each hospitalization. Incidence rates, crude and adjusted incidence rate ratios, and 95% confidence intervals were computed for patients who received infliximab and etanercept compared with those who received MTX.

Among the patients with RA who were exposed to TNFα antagonists, 850 were exposed to infliximab, and 1,412 were exposed to etanercept. The unexposed comparator cohort included 2,933 patients with RA who were treated with MTX. Etanercept users were younger (mean age 47.8 years; $P < 0.0001$ versus MTX users) than infliximab users (mean age 53.4 years; $P < 0.05$ versus MTX users) and MTX users (mean age 54.9 years). Infliximab users had more physician encounters in the 6 months prior to therapy (mean 8.2; $P < 0.0001$ versus MTX users) compared with etanercept users (mean 7.0; P nonsignificant versus MTX users) and MTX users (mean 6.9 months). The pattern of glucocorticoid usage and burden of comorbidity were similar or greater in the unexposed cohort than in the TNFα-exposed cohorts. The absolute number of cases of bacterial infection, person-time, incidence rates, and incidence rate ratios are presented in Table 1. As shown, the incidence of a serious bacterial infection was highest during the first 6 months after initiation of a TNFα antagonist, and this finding was significant only among patients exposed to infliximab. There were no significantly increased risks of infection in either the infliximab or etanercept group after the first 6 months following initiation. In our sensitivity analysis using shorter exposure windows, results were similar (data not shown).

Our results may help, in part, to explain discordance between the results of prior studies of the risk of bacterial infections associated with TNFα antagonists (1–5). Some of this discordance may result from differences in the patient populations, the methods of outcome ascertainment, use of disease-modifying antirheumatic drugs by patients who were not exposed to TNFα antagonists, and the pattern of glucocorticoid use. Based on our results, and adding to this list of factors that may affect associations with biologic agent—related infection, we now suggest that the proportion of individuals exposed to antibody-based TNFα antagonists and the proximity to the time of initiation of the TNFα antagonist may be important factors to consider, although further work is needed to confirm this observation.

We hypothesize that our finding of a significantly increased early risk of infection among individuals exposed to infliximab may relate to the large induction doses routinely given in the first 6 weeks of therapy, although more complex biologic mechanisms such as the ability to bind transmembrane TNF may be important as well. Parenthetically, we note that a similar differential pattern of infection risk has been observed for mycobacterial infection (6). The reduced risks of infection seen with both infliximab and etanercept after 6 months of therapy may also reflect a reduction in the number of patients who are highly susceptible to infection, whereby individuals who experience a serious infection early in the course of therapy may discontinue the drug and no longer be at risk of an infection in later time periods, resulting in a "healthier" cohort later in time. Additionally, it is possible that better control of inflammation with the use of TNFα antagonists ultimately leads to better longer-term outcomes, including a reduced risk of infection.

In summary, we observed that a significantly increased risk of infection occurred shortly after initiation of therapy with a TNFα antagonist; this risk was greatest for patients receiving infliximab, and it did not persist beyond 6 months. Although our overall results may raise concerns about how to balance safety with effectiveness for this important group of agents, this concern is tempered by the relatively low absolute incidence of infection, even within early time periods (incidence rate less than 5 infections per 100 patient-years). Moreover, TNFα antagonists have dramatic efficacy for a majority of patients with RA, and, for many, the expected benefits likely will outweigh even modestly increased risks of associated adverse events.

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Table 1. Incidence rates, crude and adjusted incidence rate ratios, and 95% confidence intervals for bacterial infection in patients treated with infliximab and etanercept compared with MTX, according to time since initiation of TNFα antagonist treatment*

	Infliximab	Etanercept	MTX
Less than 6 months since initiation			
Bacterial infection, no.	16	12	20
Person-time, years	372	602	1,197
Incidence rate/100 person-years	4.30	1.99	1.67
95% confidence interval	2.46–6.98	1.03–3.48	1.02–2.58
Crude incidence rate ratio	2.57	1.19	Referent
95% confidence interval	1.33–4.96	0.58–2.43	–
Adjusted incidence rate ratio†	2.40	1.61	–
95% confidence interval	1.23–4.68	0.75–3.47	–
More than 6 months since initiation			
Bacterial infection, no.	10	19	34
Person-time, years	620	1,414	2,195
Incidence rate/100 person-years	1.61	1.34	1.55
95% confidence interval	0.77–2.97	0.81–2.10	1.11–2.22
Crude incidence rate ratio	1.04	0.87	Referent
95% confidence interval	0.51–2.10	0.50–1.55	–
Adjusted incidence rate ratio†	1.14	1.37	–
95% confidence interval	0.55–2.24	0.74–2.53	–

* MTX = methotrexate; TNFα = tumor necrosis factor α.
† Adjusted for age and number of physician visits in the 6 months prior to the index date.

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