

## Tuberculosis Infection in Patients With Rheumatoid Arthritis and the Effect of Infliximab Therapy

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**Objective.** According to the Centers for Disease Control and Prevention, the 1999 and 2000 incidence rates for tuberculosis (TB) in the US population were 6.4 and 5.8, respectively, per 100,000 persons. Recently, reports of TB following infliximab administration have raised questions regarding the rate of TB in patients with rheumatoid arthritis (RA) generally and in those treated with infliximab in clinical practice. We undertook this study to determine the baseline rate of TB in RA prior to the introduction of infliximab and to determine the rate of TB among those currently receiving infliximab.

**Methods.** We surveyed patients with questionnaires, followed by detailed validation from medical records and physician reports. In study 1, we evaluated 10,782 RA patients in 1998–1999 prior to the widespread use of infliximab. In study 2, we evaluated 6,460 infliximab-treated patients in 2000–2002.

**Results.** In study 1, the lifetime rate of TB was 696 per 100,000 patients (95% confidence interval [95% CI] 547–872). Of these cases, 76.8% occurred prior to the onset of RA. During the period of prospective followup, 1 case of TB developed during 16,173 patient-years of followup, yielding a rate of 6.2 cases (95% CI 1.6–34.4) per 100,000 patients. In study 2, the TB incidence rate among infliximab-treated patients was 52.5 cases (95% CI 14.3–134.4) per 100,000 patient-years of exposure. Three of the 4 cases occurred in patients with a history of TB exposure, and no cases occurred in persons with recent TB skin tests or prophylaxis.

**Conclusion.** The rate of TB is not increased in RA patients generally. Among infliximab-treated patients, the rate is 52.5 cases (95% CI 14.3–134.4) per 100,000 patient-years of exposure. A thorough medical history regarding TB, as well as tuberculin testing and radiographic examination (if indicated), should be an essential component of anti-tumor necrosis factor therapy.

The rate of tuberculosis (TB) in patients with rheumatoid arthritis (RA) is unknown. Until recently, reports of TB in RA have been confined to case reports and case series, usually calling attention to the association of TB with specific treatments such as corticosteroids, methotrexate, and cytotoxic combinations (1–9). The issue of TB incidence and prevalence became more important with the introduction into clinical medicine of infliximab, an anti-tumor necrosis factor (anti-TNF) agent, for it soon became apparent that the cases of TB were occurring at what seemed to be an unexpected rate among those using this therapy for treatment of RA and Crohn's disease (10). In the report by Keane et al from the US Food and Drug Administration (FDA) (10), TB was identified using the MedWatch program (11) and reports from the manufacturer. The spontaneous reports used by MedWatch come predominantly from health care providers, and usually represent underestimates. The FDA report concluded that "the estimated rate of tuberculosis among patients with rheumatoid arthritis in the United States who have received infliximab therapy within the previous year is 24.4 cases per 100,000." According to the Centers for Disease Control and Prevention (CDC), the 1999 and 2000 incidence rates for TB in the US population were 6.4 and 5.8, respectively, per 100,000 persons (12,13).

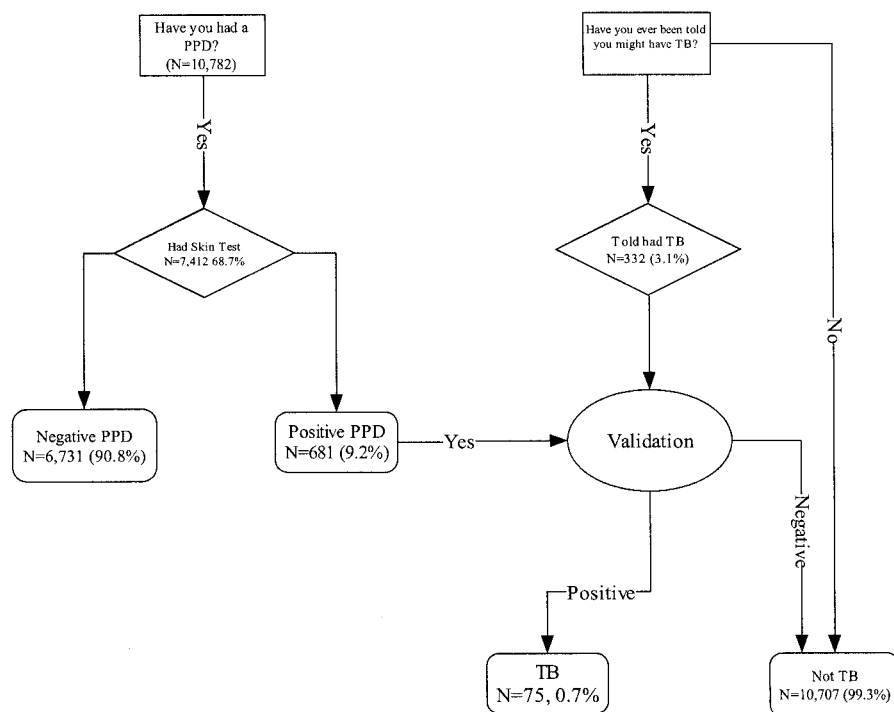
However, it is not possible to extrapolate TB rates from US population data to RA patients, for TB rates are related to many factors. Rates may differ according to race, social class, education, country of birth, age, and sex, as well as to RA itself and to

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**Figure 1.** Details of study 1 methodology. PPD = purified protein derivative; TB = tuberculosis.

comorbid illnesses and treatment with drugs such as corticosteroids.

To elucidate the issue of TB in RA, we first investigated the lifetime and current rates of TB in 10,782 RA patients participating in an outcome study of RA. These data, which reflected the assessment of patients from 1998 through 1999, were reported in abstract form in 2001 (14). Infliximab first became widely available in 2000. In this report, we combine the original 1998–1999 report with a followup study of TB rates in 2000–2002 to obtain a more complete picture of the risk of TB prior to and after the introduction of infliximab.

## PATIENTS AND METHODS

This report concerns two studies conducted by the National Data Bank for Rheumatic Diseases (NDB). Investigators in study 1 evaluated patients during three consecutive 6-month periods from July 1, 1998 through December 30, 1999, a time prior to the widespread use of infliximab for treatment of RA. Study 1 concerned 10,782 patients and included information regarding current and lifetime history of TB. This study was reported in abstract form at the American College of Rheumatology 2001 Annual Scientific Meeting (14). Study 2 covered five consecutive 6-month periods from January 2000

through June 2002. During this period, the NDB established a safety registry for infliximab. Of the 15,940 patients evaluated by the NDB during this period, 6,460 received infliximab, although not necessarily at the time of entry into the database. The main purpose of study 2 was to determine the rate of TB among RA patients treated with infliximab. Patients in both studies were geographically dispersed participants in the NDB rheumatic disease outcome project (15), and they had been diagnosed as having RA and referred to the NDB by their rheumatologists. A total of 907 US rheumatologists referred patients in studies 1 and 2. The details of the NDB projects have been reported previously (16–18).

NDB participants are asked to complete semiannual, detailed, 28-page questionnaires about all aspects of their illness. At each questionnaire assessment, demographic variables were recorded, including age, sex, ethnic origin, education level, and current marital status. Study variables included the Stanford Health Assessment Questionnaire functional disability index (HAQ disability) (19,20), pain on a visual analog scale (VAS), global disease severity on a VAS, sleep disturbances and fatigue (each on a VAS) (21), and the Short Form 36 (SF-36) mental and physical component scales (MCS and PCS, respectively) (22). To measure “health quality of life,” or QOL, we used the VAS from the EuroQol (23,24). For all except the SF-36 PCS and MCS and the EuroQol VAS, higher scores indicate more abnormality. Patients also recorded the reasons for each hospitalization, and copies of the hospital records were obtained for any hospitalization that was

in any way related to infection. All rheumatic and nonrheumatic treatment data were also obtained.

In addition, a specific set of questions relating to TB was included for study 1. Question 1 read: "Have you ever had a tuberculin test? (This is a skin test for tuberculosis.) It is sometimes called a Tine test or PPD." Question 2 read: "If you have had a tuberculin test, Tine test or PPD, or if you have had more than one tuberculin test, Tine test or PPD, was any test that you had, positive (+) [ ] negative (-) [ ]?" Question 3 read: "Were you ever told that you might have tuberculosis?" In study 2, the questions were changed to ask patients specifically whether they had been diagnosed as having TB during the preceding year and whether they had had a TB skin test during that period.

Based on the responses to these 3 questions, additional validation procedures were undertaken. Figure 1 describes the followup procedure for identifying TB cases in study 1. Patients with positive responses to questions 2 and 3 received a followup questionnaire and, where required, telephone followup contact in which they were asked detailed questions regarding how TB had been diagnosed and what treatment they had received. Patients who had not received treatment for TB were not considered to have had active TB. Patients reporting treatment for TB on the followup questionnaire were studied further to determine whether the putative treatment was a recognized TB treatment, whether it represented prophylaxis for TB based on a positive finding on the skin test, or whether it represented treatment for active TB. For patients with possible TB, we attempted to obtain hospital or medical records when appropriate. However, in many instances, such records could not be obtained because the reported illness had occurred many years previously and records were not available. In study 2, all patients who reported TB or receiving anti-TB therapy underwent detailed followup. In addition to following up on all positive reports, all hospital records on all patients during the survey period were screened for TB-related International Classification of Diseases codes regardless of their TB report status.

For study 1, patients were classified as having active TB if they reported symptoms compatible with pulmonary disease and received anti-TB treatment, or if there was other acceptable documentation for a pulmonary or nonpulmonary TB illness. We differentiated between treatment for active TB and TB prophylaxis treatment. Patients who were told only that they had had TB in the past were not classified as having active TB for this study. For study 2, documentation by a physician or by medical records was required for diagnosis.

Univariate and multivariate logistic regression were used to identify predictors of active TB. We used Stata Statistical Software (Releases 7.0 and 8.0; Stata Corporation, College Station, TX). *P* values less than or equal to 0.05 were considered significant.

## RESULTS

### Characteristics of study 1 and study 2 samples.

*Study 1.* As shown in Table 1, ~91% of patients were non-Hispanic whites, while 70.9% of people in the US were non-Hispanic whites according to the 2000 US

**Table 1.** Demographic and treatment characteristics of 10,782 rheumatoid arthritis patients in study 1 and 6,460 infliximab-treated patients in study 2\*

Variable	Study 1: all patients	Study 2: infliximab- treated patients
Age, mean $\pm$ SD years	59.8 $\pm$ 13.2	61.4 $\pm$ 13.1
Disease duration, mean $\pm$ SD years	13.2 $\pm$ 10.7	14.0 $\pm$ 10.8
Women	8,291 (76.9)	4,750 (73.5)
Ethnic origin		
Non-Hispanic white	9,801 (90.9)	6,096 (94.4)
African American	442 (4.1)	232 (3.6)
Asian American	129 (1.2)	66 (1.0)
American Indian	97 (0.9)	73 (1.1)
Hispanic	270 (2.5)	153 (2.4)
Other	54 (0.5)	20 (0.3)
Education		
0–11 years	1,283 (11.9)	757 (11.7)
12 years	4,140 (38.4)	2,523 (39.1)
>12 years	5,359 (49.7)	3,360 (52.0)
Household income, median \$	35,000	35,000
Current therapy		
Prednisone	5,887 (54.6)	3,253 (50.4)
Leflunomide	3,644 (33.8)	1,116 (17.3)
Methotrexate	5,165 (47.9)	4,821 (74.6)
Etanercept	1,240 (11.5)	505 (7.8)
Infliximab	75 (0.7)	5,345 (82.7)
Severity variables, mean $\pm$ SD scores		
HAQ disability, 0–3	1.1 $\pm$ 0.7	1.2 $\pm$ 0.7
Pain, 0–10 VAS	3.9 $\pm$ 2.8	4.1 $\pm$ 2.7
QOL, 0–100 VAS	64.2 $\pm$ 21.9	66.4 $\pm$ 20.0
SF-36 PCS	33.1 $\pm$ 8.7	30.2 $\pm$ 9.7
SF-36 MCS	43.7 $\pm$ 13.8	42.0 $\pm$ 13.7

\* Except where indicated otherwise, values are the number (%) of patients. Data are from a randomly selected observation. All patients in study 2 received infliximab, but only 80.5% were receiving it in the studied observation. HAQ = Health Assessment Questionnaire; VAS = visual analog scale; QOL = quality of life (see refs. 23 and 24); SF-36 PCS = Short Form 36 physical component scale; SF-36 MCS = Short Form 36 mental component scale.

Census (25). The median income was \$35,000, and 88.1% of patients had at least a high school education. Almost 50% had more than a high school education. Prednisone was currently being taken by 54.6% of patients at a median dose of 5 mg/day; ~90% were taking  $\leq$ 10 mg/day, and 93% were taking  $\leq$ 15 mg/day. Infliximab was being taken by 0.7% of patients, but infliximab had only recently been introduced for treatment of RA. Etanercept was being taken by 11.5% of patients. Severity variables reflected ongoing RA illness, including a mean HAQ score of 1.1 and a mean EuroQol score of 64.2.

*Study 2.* Results in study 2 were similar, with the following slight exceptions. Infliximab-treated patients were slightly older, and fewer of them were women. Physical (PCS and HAQ) and mental (MCS) function

**Table 2.** Rates of tuberculin testing, positive findings on the tuberculin tests, and active tuberculosis (TB) in 10,782 rheumatoid arthritis (RA) patients (study 1) prior to introduction of infliximab\*

TB status	
Tuberculin test	
Had a tuberculin test	7,412 (68.7)
Positive tuberculin test finding	681 (9.2)
Active TB	
Patients told they might have TB	332 (3.1)
Development of TB prior to RA onset	8,281 (76.8)
Development of TB after RA onset	2,501 (23.2)
Lifetime rate (95% CI) of active TB per 100,000 patients	696 (547–872)
Incidence rate (95% CI) of TB per 100,000 patients during 16,173 patient-years of observation	6.2 (1.6–34.4)

\* Except where indicated otherwise, values are the number (%) of patients. 95% CI = 95% confidence interval.

scores, as well as pain scores, were slightly more abnormal among infliximab-treated patients, but QOL was slightly better.

**TB-related rates.** As shown in Table 2 for study 1, ~69% of patients had undergone tuberculin testing, and 9.2% of those patients were positive for TB, rates that are consistent with those previously reported (26). After careful screening, it was determined that 75 patients (696 per 100,000, 95% confidence interval [95% CI] 547–872) had had active TB during their lifetimes. Of these cases, 76.8% had occurred prior to the onset of RA. The mean  $\pm$  SD age at RA onset was  $46.3 \pm 15.2$  years. During the period of prospective followup, 1 case of TB developed during 16,173 patient-years of followup, yielding a rate of 6.2 cases (95% CI 1.6–34.4) per 100,000 patients. In addition, no patient was hospitalized for TB during this period.

**Factors associated with TB.** Table 3 indicates that compared with non-Hispanic whites, other ethnic groups had a greater lifetime prevalence of TB (univariate odds ratio [OR] 2.08, 95% CI 1.14–3.79). The OR for age per 10 years was 1.14 (95% CI 0.96–1.36). No association was seen for education; for male sex, the multivariate OR was 1.27 (95% CI 0.76–2.12).

**Study 2—TB in the anti-TNF era.** Of the 15,940 RA patients seen in the five 6-month periods of study 2, 2,327 received etanercept, 6,460 received infliximab, and 558 received both infliximab and etanercept. All of the cases of TB occurred in infliximab-treated patients. The results that follow apply to patients who received infliximab.

As shown in Table 4, 4 cases of TB occurred, for an overall incidence rate of 52.5 cases per 100,000

patient-years or 61.9 cases per 100,000 subjects. To make the data compatible with the FDA's estimated rate in the first year following infliximab administration, the infliximab patients with  $\leq 1$  year of infliximab exposure were studied. Table 4 shows an incidence rate of 68.7 cases per 100,000 patient-years or 72.0 cases per 100,000 subjects.

Of the 6,460 infliximab-treated patients, 5,214 enrolled in the NDB as part of the safety registry, and of those, 2,983 enrolled in the registry at the time they first started infliximab. Therefore, this latter group was studied from the very onset of therapy. Table 4 shows the point estimate for those just starting infliximab to indicate an incidence rate of 69.2 cases per 100,000 patient-years or 67.1 cases per 100,000 subjects.

Among patients starting infliximab during the last year of the study (July 2001–June 2002), 59.0% of 1,106 patients who completed a skin test questionnaire reported having a TB skin test. However, 393 patients did not reply to that question. When the missing responses are considered to be negative, the percentage of patients having a skin test falls to 43.5%. It is not clear, however, whether missing responses should be classified as negative, because the question was asked in the context of an active TB question, and it seems likely that persons without TB might have skipped the question even if they had a positive skin test. Thus, it seems more likely that the true result is closer to 59%. Only 10.0% of 761 new patients entering the NDB who were not receiving infliximab reported having a TB skin test within the last year.

**Table 3.** Predictors of active TB in 10,782 RA patients during their lifetimes (study 1)\*

Predictor variable	OR (95% CI)	P
By univariate logistic regression		
Education, years		
0–11	Referent	
12	0.65 (0.31–1.33)	0.237
>12	0.89 (0.46–1.74)	0.736
Nonwhite	2.08 (1.14–3.79)	0.017
Age, per 10 years	1.14 (0.96–1.36)	0.137
Male sex	1.30 (0.78–2.15)	0.317
By multivariate logistic regression		
Education, years		
0–11	Referent	
12	0.73 (0.35–1.51)	0.401
>12	1.04 (0.53–2.06)	0.903
Nonwhite	2.26 (1.23–4.17)	0.009
Age, per 10 years	1.17 (0.98–1.41)	0.084
Male sex	1.27 (0.76–2.12)	0.355

\* OR = odds ratio (see Table 2 for other definitions).

**Table 4.** Rate of new cases of TB among infliximab-treated patients from January 2000 through June 2002\*

Type	Cases	Patients	Patient-years	Incidence rate (95% CI)†
All patients				
By risk time	4	6,460	7,621	52.5 (14.3–134.4)
By subject	4	6,460	6,460	61.9 (16.9–158.5)
Infliximab exposure within last year				
By risk time	4	5,558	5,827	68.7 (18.7–175.7)
By subject	4	5,558	5,558	72.0 (19.6–184.2)
New starts				
By risk time	2	2,983	2,892	69.2 (8.4–249.7)
By subject	2	2,983	2,983	67.1 (8.1–242.1)

\* See Table 2 for definitions.

† Rates by risk time are per 100,000 patient-years of exposure. Rates by subject are per 100,000 subjects.

**Characteristics of patients developing TB.** As shown in Table 5, all of the patients developing TB were women, and all were older than the average age of patients in the cohort (60.8 years). One patient was receiving methotrexate and one was receiving prednisone. Three of the cases were extrapulmonary. Of interest, 3 patients had previously had a positive finding for TB on the skin test, and one had been suspected of having TB in the past. None of these patients received prophylaxis. The pre-active TB status of the fourth patient is not known. None of the patients reported having a TB skin test in 2001 or 2002 prior to symptom development. Overall, TB was significantly more likely to occur in older persons, and only occurred in women receiving infliximab.

**DISCUSSION**

With limitations, study 1 shows that the rate of TB in RA is not increased. The most important limitation regarding this conclusion consists of the ethnic/racial characteristics of the study sample, 90.9% of whom were non-Hispanic whites. However, non-Hispanic/non-Latino whites represent 70.9% of the US population. The current study population reflects the

population of RA patients who are usually seen by US rheumatologists and who are willing to participate in outcome studies. To get a further estimate of racial prevalence, we characterized 6,776 RA patients who had been invited to participate in our outcome studies, but who had declined. Non-Hispanic whites represented 84.6% of this group. Therefore, the current study over-represents non-Hispanic whites not only compared with the US population, but also compared with rheumatology practice. These findings are characteristic of survey research and medical care, since minorities are less likely to seek specialist care (27–30) and to participate in studies (31–34). It should also be noted that fewer persons in our cohort than in the US population did not complete high school (11.7% versus 15.9%).

The consequence of decreased minority participation might be the underestimation of the true rate of TB in RA. In 1999, data from the CDC National Center for HIV, STD, and TB Prevention indicated the following rates for TB per 100,000 persons: non-Hispanic white 2.2, black 16.8, Hispanic 12.4, and Asian/Pacific Islander 35.3 (13). One approach to understand the effect of underrepresentation of minorities would be to extrapolate from the rates of TB among US minorities to

**Table 5.** Characteristics of individual RA patients who developed TB\*

Age/sex	Ethnic origin	Treatment duration, months			Date TB reported	PPD†		TB site
		Infliximab	Prednisone	MTX		2001	2002	
66.9/F	White	1	0	1	8/1/2001	0	0	Extrapulmonary
65.9/F	White	7	0	0	2/6/2002	0	0	PIP joint
69.7/F	Hispanic	12	0	0	6/19/2002	0	0	Cervical node
78.2/F	White	3	1	0	8/6/2002	0	0	Pulmonary

\* MTX = methotrexate; PPD = purified protein derivative; PIP = proximal interphalangeal (see Table 2 for other definitions).

† Refers to PPD in 2001 or 2002 prior to development of TB.

those in the current study. Assuming a minority TB rate of 15.0, then 20% of that would be 3.0. Adding this value to the study TB rate of 6.2 to adjust for underrepresentation of minorities would yield a rate of 9.2 per 100,000. Alternatively, increasing the number of TB cases in our study by 1 additional case would yield a rate of 12.3 (95% CI 1.5–44.6). The 95% CI for the TB rate of 6.2 in this study (1.6–34.4) and the 95% CI at the doubled rate of 12.3 (1.5–44.6) both overlap the 1999 US non-Hispanic white TB rate (2.2 per 100,000 persons) and the overall 1999 US rate (6.4 per 100,000 persons). However, even the large sample size of this study ( $n = 10,782$ ) is too small to describe narrow CIs for uncommon illness such as TB.

Another issue in the understanding of TB rates in RA is age. The US population rates noted above reflect all ages, but the mean  $\pm$  SD age of RA patients in this study was  $59.8 \pm 13.2$  years. According to US 1999 data, the TB rates per 100,000 persons were 7.3 for persons age 25–44, 8.2 for persons age 45–64, and 11.7 for persons age  $\geq 65$  years. This suggests that the overall US rate of 6.4 per 100,000 persons may be too low in comparison with RA populations.

It is difficult to speak accurately about the effect of drug therapy on TB rates in the study 1 cohort, because the overall TB rate was low. The case that occurred in the prospective part of this study was not associated with infliximab, but too few patients were receiving infliximab at the time of study 1 for us to draw any conclusions regarding infliximab. However, more than one-half of the RA patients were receiving steroids (the median prednisone dose was 5 mg/day). If steroids or methotrexate (or even the presence of RA itself) had a substantial effect on TB rates, we would have expected to see higher rates than those we found in this study.

Study 2, however, sheds additional light on TB and the effect of infliximab. The overall rate of TB among patients receiving infliximab was 52.5 (95% CI 14.3–134.4) per 100,000 patient-years of exposure. This rate is much greater than the population rates noted above and confirms the risk associated with this treatment. In addition, cases generally occurred shortly after treatment started (Table 5). This is consistent with the Keane et al–FDA report (10), which indicated that the “. . . median interval from the start of treatment with infliximab until the development of tuberculosis was 12 weeks (range, 1 to 52).”

It is also of interest that of the 3 cases in the current study for which information regarding prior TB status was available, no patient received a skin test or prophylactic treatment, and none of the 4 patients had a skin test before developing symptoms. In contrast, no

cases of TB occurred in the 44–59% of infliximab-treated patients who received a skin test. Although the sample size is too small for us to come to definite conclusions based on our data, it would appear that it is essential to screen for TB before administering infliximab, as has been recommended by the manufacturer and authorities (10,35,36).

Do biologic differences between infliximab and etanercept influence the risk of developing TB? TNF $\alpha$  increases the ability of macrophages to phagocytose and kill *Mycobacterium*. It is also needed for formation of granulomas, which wall off mycobacteria and prevent their dissemination (37). Infliximab is a monoclonal antibody with high binding affinity and specificity for TNF. It forms stable complexes with the monomeric and trimeric forms of soluble TNF and with the transmembrane forms of TNF (37,38). Macrophage and monocyte lysis by cytotoxicity is the result of binding to transmembrane TNF $\alpha$  and depends on antibodies and complement (37–40). Compared with infliximab, etanercept forms less stable complexes with membrane-bound TNF and monomeric TNF (37,38), but binds significantly with the trimeric form of soluble TNF. Unlike infliximab, etanercept also forms stable complexes with lymphotoxin  $\alpha$ , which appears to be involved in the Th1 response to *Mycobacterium bovis* BCG infection and in spleen granuloma formation (41).

Infliximab and etanercept also differ in their modes of administration and pharmacokinetics. Etanercept is administered subcutaneously twice a week and has a half-life of  $\sim 3$  days. Infliximab is given as an intravenous infusion at weeks 0, 2, and 6, followed by infusion every 8 weeks. Infliximab has a half-life of 10.5 days. Although infliximab and etanercept both interact with TNF, there are some differences that may be important. Drug-mediated apoptosis and monocytopenia appear to be unique to infliximab (37). In addition, infliximab appears to bind more avidly to different forms of TNF (37). There is also a possibility that bolus dosing of infliximab may affect the host's ability to control *Mycobacterium tuberculosis* infection; this issue has not been studied (37). Despite the apparent increase in TB cases associated with infliximab in this study, TB has also been seen in patients treated with etanercept, and the etanercept package insert carries a warning concerning TB. The recently released anti-TNF agent, adalimumab, also carries a TB warning. This suggests the need for careful evaluation and monitoring of patients receiving anti-TNF therapy.

One additional limitation of the present study concerns the recalled lifetime occurrence of TB. Recall

may be subject to substantial error concerning the event as well as its timing. Finally, the few cases of TB identified in our studies limit meaningful multivariate analyses.

In summary, just prior to the widespread use of infliximab, the rate of TB in 10,782 RA patients followed up prospectively was 6.2 (95% CI 1.6–34.4) per 100,000 patients during 16,173 patient-years of observation. This rate is not distinguishable from the 1999 US non-Hispanic white TB rate (2.2 per 100,000 persons) and the overall 1999 US rate (6.4 per 100,000 persons). However, patients who received infliximab had a TB incidence rate of 52.5 (95% CI 14.3–134.4) per 100,000 patient-years of exposure. All cases occurred in persons without complete screening for TB and without prophylaxis.

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