Granulomatous Infectious Diseases Associated with Tumor Necrosis Factor Antagonists

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The relationship between the use of tumor necrosis factor antagonists and onset of granulomatous infection was examined using data collected through the Adverse Event Reporting System of the US Food and Drug Administration for January 1998–September 2002. Granulomatous infections were reported at rates of ~239 per 100,000 patients who received infliximab and ~74 per 100,000 patients who received etanercept ($P < .001$). Tuberculosis was the most frequently reported disease, occurring in ~144 and ~35 per 100,000 infliximab-treated and etanercept-treated patients, respectively ($P < .001$). Candidiasis, coccidioidomycosis, histoplasmosis, listeriosis, nocardiosis, and infections due to nontuberculous mycobacteria were reported with significantly greater frequency among infliximab-treated patients. Seventy-two percent of these infection occurred ≤90 days after starting infliximab treatment, and 28% occurred after starting etanercept treatment ($P < .001$). These data indicate a risk of granulomatous infection that was 3.25-fold greater among patients who received infliximab than among those who received etanercept. The clustering of reports shortly after initiation of treatment with infliximab is consistent with reactivation of latent infection.

TNF is a proinflammatory cytokine that plays an important pathogenic role in rheumatoid arthritis and other inflammatory conditions. Three TNF antagonists have been approved by the US Food and Drug Administration (FDA) for treatment of these conditions. Two, infliximab (Remicade; Centocor) and adalimumab (Humira; Abbott Laboratories), are monoclonal antibodies; the third, etanercept (Enbrel; Amgen), is a dimeric soluble TNF receptor.

Received 25 September 2003; accepted 4 January 2004; electronically published 15 April 2004.

Presented in part: 2003 Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society of Microbiology, Chicago, IL, September 2003 (poster B1521).

Financial support: Amgen.

Conflict of interest: M.S.B., M.E.H., J.Y.W. are employees of Zynx Health, which provides consulting services to biotechnology and pharmaceutical companies, including Amgen.

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Clinical Infectious Diseases 2004;38:1261–5

1058-4838/2004/3809-0011$15.00

TNF is essential for granuloma formation and maintenance, which are key components of host defenses against intracellular pathogens [1–3]. The increased clinical use of TNF antagonists has been accompanied by increased reporting of granulomatous infectious diseases, such as tuberculosis, histoplasmosis, and several less common conditions, in patients treated with these agents [4–12]. Previous reports have suggested that these infections were particularly associated with infliximab rather than etanercept [4, 7]; however, the small numbers of cases reported in these series limited the statistical power of such observations.

The FDA monitors the safety of TNF inhibitors through its Adverse Event Reporting System (AERS), a surveillance system to which drug manufacturers are required to submit reports of adverse events and to which health care professionals and consumers voluntarily send adverse event reports. To further examine the relationship between TNF antagonist use and infections normally contained by granulomas, we analyzed data from the FDA AERS from the time of approval of etanercept and infliximab through the third quarter of 2002. Infliximab was approved for the treat-

ment of Crohn disease in August 1998 and for rheumatoid arthritis in October 1999. Etanercept was approved for the treatment of polyarticular-course juvenile rheumatoid arthritis in May 1999, rheumatoid arthritis in September 1998, and psoriatic arthritis in January 2002. Adalimumab was excluded from this analysis because it was not approved for clinical use until after this period had ended (December 2002). Data from subsequent periods have not yet been released by the FDA.

MATERIALS AND METHODS

Data collection. A list of granulomatous diseases was developed on the basis of expert opinion and published literature [13]. The AERS database was searched for reports of adverse events associated with the use of infliximab and etanercept from 1998 through the third quarter of 2002 (19 quarters total). FDA AERS reports meeting these criteria were then imported in ASCII format into SAS system software, version 8.2 (SAS Institute), and analytical files were created for the final study database. Adverse event reports of $\geqslant 1$ of these infections were included in the study if they occurred in association with the use of infliximab or etanercept, regardless of the stated relationship of the event to these drugs in the report (primary suspect, secondary suspect, or concomitant). Adverse event reports in which both etanercept and infliximab were listed were excluded. When multiple reports were found to be associated with the same patient, the last report (i.e., that with the most recent report date) was selected. Multiple infections with different organisms occurring in a single individual were counted separately (e.g., *Mycobacterium tuberculosis* and *Listeria monocytogenes*). Multiple reports for the same patient in which 2 species could not clearly be differentiated (e.g., *M. tuberculosis* and mycobacteria not otherwise specified) were considered to be duplicates and were counted only once, with the most detailed report used. The temporal relationship between TNF antagonist treatment and granulomatous infection was analyzed using both the reported onset date of the infection and the date on which the report was filed in relation to the reported date of initiation of treatment. Reports were also examined for concomitant use of immunosuppressive medications. The numbers of patients treated with etanercept or infliximab as of September 2002 were determined using data reported to the FDA by the manufacturers.

Statistical analysis. Differences in proportions were examined by χ^2 analysis. In those instances in which the number of events was insufficient for χ^2 analysis, Poisson analysis was used to determine the probability of as few events occurring as were observed in the etanercept group, given the frequency observed in the infliximab group. The Wilcoxon rank sum test and Spearman rank correlation test were used to test for differences and correlations, respectively, in numeric data that were not normally distributed.

RESULTS

According to manufacturers' reports, as of September 2002, >233,000 patients in the United States had been treated with infliximab [14], and >113,000 had been treated with etanercept [15] (A. Calandra [Amgen], personal communication to J. Siegel [FDA]). As of August 2002, ~2500 individuals have been treated with adalimumab, largely in clinical trials [16]. These patients were excluded from subsequent analyses because of their relatively small number.

There were 35,275 distinct reports extracted from the AERS database, of which 716 described granulomatous infections associated with either etanercept or infliximab. Of these, 89 reports were excluded because they indicated use of both etanercept and infliximab, and 5 were excluded because they appeared to be duplicates. The remaining 622 unique reports described 639 infectious adverse events, 556 and 83 of which were associated with infliximab and etanercept, respectively. No reports were identified for the year 1998. The number of reports during subsequent years increased progressively from 13 in 1999 to 359 in the first 9 months of 2002. The proportion of etanercept-associated reports dropped progressively during the study period, from 62% in 1999 to 11% in 2002 ($P < .001$).

The demographic characteristics of the patients described in these reports are as follows. The median patient age was 60 years (interquartile range [IQR], 46–68 years) for infliximab and 58 years (IQR, 52–68 years) for etanercept. Patients were predominantly female (66% and 59% of patients in the infliximab and etanercept groups, respectively). The proportion of reports citing concomitant corticosteroid use was 41% for infliximab and 66% for etanercept; for concomitant methotrexate use, these proportions were 43% and 41%, respectively. Data on the indication for TNF antagonist treatment were available for 208 reports, beginning in 2002. In 14% of the infliximab-associated reports but in none of the etanercept-associated reports, the indication for TNF antagonist treatment was Crohn disease; otherwise, the indications were similar (data not shown). The indications for which these drugs were prescribed include off-label conditions, which resulted in the creation of several small subgroups. As a result, a comparison of infection risk with regard to indication involved numbers that were too small for meaningful statistical analysis.

The number and rate ratio of reported granulomatous infections in the 622 reports are shown in table 1. Overall, infectious adverse events were reported in ~239 per 100,000 infliximab-treated patients, compared with ~74 per 100,000 etanercept-treated patients ($P < .001$). The distributions of these infections within each of the groups of treated patients were

very similar. Infection due to *M. tuberculosis* was the most frequently reported granulomatous infection, reported in ~144 per 100,000 infliximab-treated patients and in ~35 per 100,000 etanercept-treated patients ($P < .001$). Among the other infections, candidiasis, coccidioidomycosis, histoplasmosis, listeriosis, nocardiosis, and those due to nontuberculous mycobacteria were all reported with significantly greater frequency among patients who received infliximab. No infection was reported significantly more often among patients who received etanercept. Two hundred eight infections were reported to have occurred without concomitant use of immunosuppressive medications; of these, 189 were associated with infliximab treatment and 19 were associated with etanercept treatment. In these reports, tuberculosis was also the most common infection reported.

Three hundred forty-five reports provided data indicating the occurrence rates of adverse events. These data were stratified by 90-day periods of risk and are shown in figure 1, expressed as the number of cases per 100,000 treated patients for each drug. The median time to onset of adverse events was 40 days for infliximab (274 patients) and 236 days for etanercept (71 patients; $P < .001$). Seventy-two percent of infliximab-associated infections occurred within the first 90 days of treatment, compared with 28% for etanercept ($P < .001$). For tuberculosis, these values were 47.3% and 12.5%, respectively ($P < .001$). The time from onset of treatment to the date on which the event was reported could be calculated in 492 reports. This interval was also significantly shorter among patients who received infliximab versus those who received etanercept (median duration, 190 days vs. 511 days; $P < .001$). Twenty-two percent of infliximab-associated cases were reported ≤90 days after initiation of treatment, compared with no reports in the etanercept group during the same period ($P < .001$).

DISCUSSION

This study represents the largest, most systematic report to date of the infectious complications of TNF antagonists. In it, 374 reported cases of tuberculosis, 42 of histoplasmosis, and 223 other granulomatous infections were identified in ~346,000 US patients treated over a 4.75-year period. The main findings were that granulomatous infections after treatment with infliximab were reported at a rate >3 times that of etanercept and that these excess reports were clustered within the first 3 months after initiating treatment.

The voluntary nature of physician reports to the AERS and

Table 1. Pathogens that caused granulomatous infections in US patients who received infliximab or etanercept.

Pathogen, type of infection	Infliximab group (n = 233,000)	Etanercept group (n = 113,000)	Rate ratio	P
Mycobacterium tuberculosis	335 (143.8)	39 (34.5)	4.17	<.001[a]
Histoplasma capsulatum	39 (16.7)	3 (2.7)	6.30	<.001[b]
Candida species				
Any	38 (16.3)	8 (7.1)	2.30	.006[b]
NS	26 (11.2)	7 (6.2)	1.80	.065[b]
Systemic	10 (4.3)	1 (0.9)	4.85	.046[b]
Listeria species	36 (15.5)	2 (1.8)	8.73	<.001[b]
Mycobacterium species (NS)	30 (12.9)	7 (6.2)	2.08	.023[b]
Aspergillus species	29 (12.4)	10 (8.8)	1.41	.17[b]
Cryptococcus species	11 (4.7)	8 (7.1)	0.67	.91[b]
Nocardia species	10 (4.3)	1 (0.9)	4.85	.046[b]
Salmonella species	7 (3.0)	4 (3.5)	0.85	.75[b]
Toxoplasma species	5 (2.1)	0 (0)	…	.088[b]
Brucella species	2 (0.9)	0 (0)	…	.38[b]
Bartonella species	1 (0.4)	0 (0)	…	.62[b]
Leishmania species	1 (0.4)	0 (0)	…	.62[b]
Mycobacterium leprae[c]	1 (0.4)	0 (0)	…	.62[b]
Overall	556 (238.6)	83 (73.5)	3.25	<.001[a]

NOTE. Data are no. of patients (no. per 100,000 patients who received the drug). NS, species was not specified.

[a] By χ^2 analysis.
[b] By Poisson analysis.
[c] Resulted in leprosy.

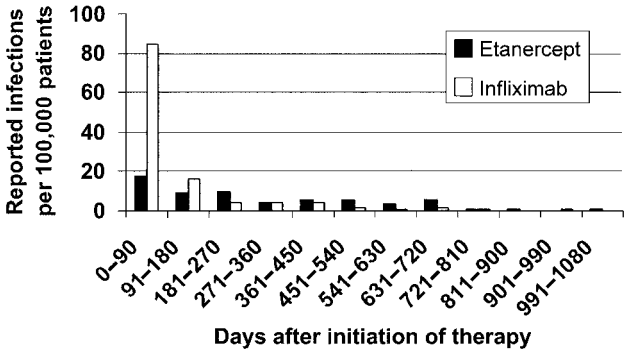

Figure 1. Time distribution of granulomatous infections during treatment with etanercept or infliximab, expressed as reports per 100,000 treated patients ($n = 345$).

the lack of geographic or ethnic data place some limitations on this analysis. Adverse events occurring soon after initiating a new therapy may be more likely to be reported, introducing a potential source of bias. The reported annual incidence of coccidioidomycosis, listeriosis, and tuberculosis in the United States during the year 2001 were ~1.4, ~0.5, and ~5.6 per 100,000 population, respectively [17, 18]. These illnesses are not distributed uniformly throughout the general population in the United States, however. One-half of all tuberculosis cases in the United States now occur among those who are foreign born, with an incidence of ~27 per 100,000 population. For this reason, tuberculosis cases tend to be concentrated in major ports of entry, such as New York, Florida, Texas, and California. Without additional geographic and demographic data, the true risk of tuberculosis posed by either etanercept or infliximab with respect to the general population cannot be accurately assessed. However, the other infliximab-associated infections differ substantially from tuberculosis in their geographic dispersion. Histoplasmosis, for example, occurs mainly in the central United States, coccidioidomycosis occurs mainly in the southwest, and nontuberculous mycobacterial infection occurs mainly in the southeast. A major outbreak of listeriosis occurred in the northeast United States during the period of data collection [19]. Other infections, such as candidiasis and nocardiosis, do not vary substantially in their regional incidence. All these infections were reported at a greater rate for infliximab than for etanercept. It therefore is unlikely that different geographic patterns of use for these drugs could have accounted for the difference in the number of reported infections observed between infliximab and etanercept.

Diseases such as tuberculosis and histoplasmosis may arise after recent infection or from reactivation of latent infection that occurred years or even decades earlier. Indeed, the increased rates of tuberculosis among foreign-born individuals reflect the greater prevalence of latent *M. tuberculosis* infection outside of the United States. In the current study, excess tuberculosis cases were observed during the first 3 months of infliximab treatment, compared with etanercept treatment, in both time-to-onset and time-to-report-date analyses. The annualized risk of tuberculosis during this interval (0.27%) is 8 times higher than the estimated annual risk of new *M. tuberculosis* infection in the United States (0.03%) [20, 21]. These excess cases therefore most likely reflect reactivation of latent infection.

Despite sharing a common therapeutic target, these findings indicate that infliximab and etanercept differ in their effects on preexisting granulomas. This observation is consistent with recent reports that infliximab but not etanercept is effective in the treatment of granulomatous chronic inflammatory conditions such as Crohn disease, sarcoidosis, and Wegener granulomatosis. The biologic basis of this difference is not certain. The dosage interval for infliximab is substantially longer than its half-life, and, although affinity measurements for these molecules are particularly complex because of the multiple binding sites on each, the monoclonal antibodies may have significantly higher affinity for TNF [22]. However, the in vitro data often describe conflicting results [23–25]. The high peak levels and high binding affinity of infliximab may have contributed to the differences we observed in infection risk. In addition, infliximab readily binds transmembrane TNF; in vitro, this may lead to cell lysis via complement-dependent cytolysis and antibody-dependent cell-meditated cytotoxicity [22]. In vivo, infliximab has been shown to induce apoptosis of monocytes and T cells [26, 27]. Defects in host immunity resulting from cell death may be expected to be more pronounced and less readily reversible than those due simply to TNF neutralization. This may account for the greater efficacy of infliximab in the treatment of some conditions such as Crohn disease. Further studies are needed to examine these questions.

The FDA has required that package inserts for Remicade (infliximab) and Humira (adalimumab) carry "black box" (high-level) warnings about the risk of tuberculosis and other opportunistic infections. These warnings recommend that patients undergo skin testing for latent tuberculosis infection and that treatment of latent infection be initiated before initiation of tuberculosis therapy. Although sound, this approach has important limitations. Skin test reagents are not available for many of the infections identified in this study other than those due to *M. tuberculosis.* Even for tuberculosis, this strategy can only be partially effective, because skin tests may have falsely negative results for patients with rheumatoid arthritis, even when performed before initiation of treatment with corticosteroids or disease-modifying drugs [28–33]. As a result, physicians should use clinical judgment when initiating treatment in patients from regions where these diseases are common.

Acknowledgments

We thank Lisa Kaspin and Hoang Luu, for assistance with the preparation of the article in manuscript, and Kristina Chen, for technical assistance.

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