Conflict of interest. D.B.: No conflict.

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Inconsistencies in Reporting of Granulomatous Infectious Diseases Associated with Infliximab and Etanercept

Sir—The article by Wallis et al. [1], in which it is concluded that granulomatous infectious diseases occur more often in patients receiving infliximab, than in patients receiving etanercept, contains major inconsistencies that make the conclusions invalid. Table 1 of the article [1] purports to show the number of patients in the United States receiving infliximab or etanercept who had granulomatous infections reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS). The authors overlooked, however, that this database includes not only voluntarily reported cases from the United States, but also cases reported worldwide. On the basis of our own analysis [2], as well as that of the FDA [3], approximately two-thirds of worldwide reported cases of tuberculosis (TB) in patients receiving infliximab are from outside the United States. Therefore, table 1 in the article [1] overstates the number of reported cases of TB in patients receiving infliximab in the United States by at least 3-fold. In contrast, because of limited use of etanercept outside of the United States, especially during the study period, the majority of TB cases reported in patients receiving etanercept are from the United States [4]. TB was the most frequently reported granulomatous infection for both patients receiving infliximab and those receiving etanercept, making the aggregate analyses reported by Wallis et al. [1] for all granulomatous infectious also erroneous. Furthermore, because the numerators are based on cases reported worldwide and the denominators pertain to cases reported in the United States only, the reporting rates in the report are erratic as well.

In the United States and most other countries, there are no regulations that require health care providers to report adverse events, and consequently, the data in spontaneous reporting systems, such as the FDA-AERS database, are generated in an uncontrolled and incomplete manner. A number of biases, usually unknown, can affect reporting [5, 6]. These biases might be different between products and, as the FDA has pointed out [6], require that extreme caution be exercised when comparing reporting rates; in fact, such com-

Figure 1. Cumulative proportion of tuberculosis (TB) cases in relation to start of anti-TNF treatment. Each symbol represents a case reported to the US Food and Drug Administration Adverse Event Reporting System from January 1998 through March 2003. The 2 curves differed by Kaplan-Meier analysis (P = .00028). The infection in the curve at 90 days of infliximab therapy is consistent with a shift in etiology at that time from reactivation of disease to rapid progression of new infection.

infliximab was 95 cases per 100,000 person-years, compared with 11 cases per 100,000 person-years for etanercept. The overall TB incidence in the United States (reflecting both reactivation and progression of new infection) at the time of this study was 5.8 cases per 100,000 person-years [3]. Thus, despite the inherent shortcomings of postlicensing surveillance data, we believe that our conclusion—namely, that the risk of reactivation of TB is greater with infliximab therapy than with etanercept therapy—is correct.
parisons should merely be considered exploratory or hypothesis-generating [6]. Moreover, because of the incompleteness of data, especially regarding potential confounding variables, logistic regression analyses to adjust for baseline imbalances cannot be adequately performed. Therefore, unraveling the relative contribution of intrinsic TB susceptibility, other immunosuppressive medication, comorbidities, and the TNF-α antagonists to the development of TB and the other events is impossible with data from the FDA-AERS database. Because of the major inconsistencies in Wallis et al. [1], and the limitations inherent to data in the FDA-AERS database, the conclusions of the article are not supportable.

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References


Reply to Schaible

SIR—Schaible [1] is correct that our original analysis [2] improperly included cases arising outside of the United States. The Adverse Events Reporting System (AERS) database that we obtained under the Freedom of Information Act came from the US Food and Drug Administration essentially without guidance or instruction. We hope that other investigators using this invaluable resource will benefit from our error and avoid this mistake in their research. A revised analysis of these data appears elsewhere in this issue of Clinical Infectious Diseases [3]. As it indicates, the difference between infliximab and etanercept persists for tuberculosis (TB) and several other granulomatous infections after the removal of data for foreign cases. Furthermore, this difference is amplified when one focuses on the initial 90 days of anti-TNF therapy. Accelerated onset of TB is closely linked to increased overall TB risk for other immunosuppressive conditions, such as AIDS. Time from initiation of anti-TNF therapy to onset of TB is a robust parameter that is unlikely to be compromised by the uncertainties that are inherent in other aspects of the AERS database. We therefore believe that our conclusion—that the risk of reactivation of TB is greater with infliximab than with etanercept—is correct.

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