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.

Acknowledgment

Conflict of interest. T.F.S. is an employee of Centocor, an operating company of Johnson & Johnson. Centocor is the manufacturer of Remicade (infliximab).

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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) data 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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Conflict of interest. R.S.W. has served as a consultant for Amgen and is the recipient of a research grant from Wyeth. M.B. and J.W. are former employees of Zynx Health, a subsidiary of the Cerner Corporation. Zynx Health provides consulting services to biotechnology and pharmaceutical companies, including Amgen, which provided grant support for the original study [1]. D.B.: No conflict.

Tuberculosis Cases Associated with Infliximab and Etanercept

Sir—We write with regard to the article “Granulomatous Infectious Diseases Associated with Tumor Necrosis Factor Antagonists” by Wallis et al. [1]. This article makes important contributions to the scientific literature about the infectious complications, particularly tuberculosis (TB), associated with these effective biologic agents. The US Centers for Disease Control and Prevention (CDC; Atlanta, GA) anticipates that this issue will have emerging public health importance since these agents are employed more widely. Wallis and colleagues have reviewed the US Food and Drug Administration (FDA) adverse events database and have shown that, on a rate basis, more TB cases are associated with infliximab than with etanercept. Furthermore, they found that the onset of TB in these cases occurs sooner after drug administration with infliximab than with...
etanercept. They concluded that the risk of TB is greater with infliximab than with etanercept.

The authors base their conclusion, in part, on comparing the incidence rates of reported TB cases associated with these drugs. We agree that, as presented, the data suggest a greater risk of TB with infliximab, but we call attention to a potential misunderstanding in the methods. Wallis et al. [1] state that the denominators for their incidence calculations contain only persons who initiated treatment with infliximab or etanercept in the United States, but they do not state whether the numerator is similarly limited to TB reports from the United States. Although the FDA adverse events database is in the United States, the system accepts adverse event reports from both within and outside the country, and many of the cases of TB collected in this database are from outside the country. Having recently reviewed this database, we suspect that Wallis et al. [1] included case reports from both the United States and other countries in the numerator and included only persons who initiated treatment in the United States in the denominator.

This possibility leads to an overestimation of TB risk associated with any of these agents, and it underscores the difficulty in drawing conclusions about a risk difference between agents. Although other reports [2] also suggest that infliximab carries a greater risk of TB disease, to date, there has been no study directly comparing the rates of TB disease associated with these 2 agents while controlling for potential differences in TB risk factors among patients. Fewer TB cases have been reported with etanercept, but the clinical features of these cases (with the exception of a shorter time to disease onset with infliximab, as noted above) resemble those associated with infliximab. With either agent, TB is often extrapulmonary and disseminated [3].

We consider both agents, as well as other TNF-α antagonists, as immunosuppressive drugs that confer a risk of TB. Any person who is a candidate for TNF-α antagonist therapy should be screened for latent Mycobacterium tuberculosis infection with a medical history, a tuberculin skin test, and a chest radiograph, in accordance with CDC guidelines [4–6]. Persons who have latent infection diagnosed should begin preventive therapy before starting treatment with TNF-α antagonists, and clinicians should remain vigilant for TB in any patient who has a febrile or respiratory illness while receiving any TNF-α antagonist.

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