LETTER TO THE EDITOR

Anti-tuberculosis treatment and infliximab

It was with considerable interest that I read the case report of Vlachaki et al., 1 “Delayed response to anti-tuberculosis treatment in a patient on infliximab”, in the May 2005 issue of your journal. However, I believe the authors' main conclusion, that the prolonged illness was due to prolonged anti-TNF activity of infliximab, is incorrect. Instead, I believe it is much more likely that it represents immune reconstitution inflammatory syndrome (IRIS) due to infliximab withdrawal.

IRIS, or paradoxical worsening, typically presents as hectic fevers, lymphadenopathy, worsened pulmonary infiltrates, effusions, hypoxia, and occasionally, the evolution of new lesions not clinically apparent prior to starting treatment. IRIS occurs in its most complete form in persons starting treatment for both AIDS and tuberculosis, 2-7 but has also been described in the context of other HIV-associated infections, and in patients with tuberculosis without HIV infection. 8-10 In AIDS cases with tuberculosis, IRIS onset is closely related temporally to the initiation of antiretroviral therapy (ART). 3 Baseline risk factors for IRIS in AIDS/TB include disseminated or extrapulmonary tuberculosis, low initial CD4 count, and non-reactive tuberculin skin tests. Patients with a vigorous response to ART (as assessed by changes in viral load or CD4 count) are also at increased risk. 3,11 Little is known regarding the immunology of IRIS, except that nearly all cases convert to strongly reactive tuberculin skin tests as the syndrome evolves. 1,3 There are no specific diagnostic tests for IRIS. However, it is a clinical hallmark of IRIS that the magnitude of the host immune response is disproportionate to the burden of infection, which in TB-associated cases, usually has declined substantially by the time IRIS is diagnosed.

Infliximab (anti-TNF monoclonal antibody) is licensed in the US for treatment of Crohn’s disease and rheumatoid arthritis. It is administered periodically by intravenous infusion, usually every 4-6 weeks. In addition to blocking soluble TNF, infliximab inhibits T cell activation and interferon γ expression. 12,13 Its combined effects on TNF and IFNγ may account for the high risk infliximab poses for reactivation of latent TB infection, which has been estimated in Europe to be as high as 173 cases per 100,000 persons per year. 14 This risk is significantly greater than that of etanercept, 15,16 a soluble TNF receptor that does not block IFNγ expression. 13

A recent retrospective study by Garcia Vidal et al. 17 described typical IRIS-type paradoxical reactions due to withdrawal of infliximab following the diagnosis of tuberculosis in four patients with autoimmune diseases. All four patients presented with disseminated or extrapulmonary tuberculosis and subsequently had infliximab treatment discontinued. The interval until IRIS occurrence was from 5 to 16 weeks; however, this may have been influenced by the case definition, which required an interval of at least 4 weeks for inclusion in the study. Three of the four cases required corticosteroids or surgical intervention.

In the present case report, Vlachaki attributes the delayed therapeutic response to “the long term immunosuppressive action of infliximab”. It is not clear how the authors made this assessment, since the tuberculin skin test was not repeated, nor were any in vitro tests performed to measure mycobacterial T cell responses. Indeed, the return of active spondylitis would appear to indicate a lack of prolonged effect. The authors implied that immunity is required for sterilization of mycobacterial infection, and that the delayed resolution of the granulomatous host response must therefore indicate delayed resolution of infection. However, they report the results of four bronchoscopic diagnostic procedures, performed at diagnosis, and after 20 days, 3 months, and 12 months of treatment. Specimens from the first procedure were positive for Mycobacterium tuberculosis by both stain and culture; those from the second, by culture only. Subsequent specimens were negative. This cannot be described as a delayed microbiologic response to therapy.

More importantly, the concept that host immunity facilitates sterilization during TB chemotherapy is not likely correct. The capacity of human...
Macrophages to kill virulent *M. tuberculosis* is very limited. Granulomas therefore serve to contain an infection that cannot otherwise be eradicated by host defenses. Mycobacteria contained within granulomas face a hostile microenvironment with low pH, oxygen, and other nutrients. Sequestered mycobacteria adapt to these harsh conditions with profound alterations in gene expression profiles, resulting in reduced replication and reduced aerobic metabolism. This adaptation forms the basis of clinical latency in tuberculosis. Granulomas may thus paradoxically protect sequestered mycobacteria from administered chemotherapy by reducing drug penetration, and by reducing the level of expression of the molecular targets of these drugs. Experimental evidence indicating antagonism between immunity and sterilization in tuberculosis is summarized in Table 1. The report most pertinent to the case in question is that of Narita et al., a retrospective case-control study of AIDS/TB IRIS. The authors found that IRIS increased by six fold the subsequent risk of TB relapse.

Based on this evidence, there is reason to believe that infliximab may hasten, rather than delay, the clinical and microbiologic response to tuberculosis therapy, and that its withdrawal at the time of TB diagnosis may be problematic. Further studies of the management of tuberculosis in patients on infliximab therapy are warranted.

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