Tuberculosis and TNF–α inhibitors—Dangerous liaisons?

Therapeutic interventions in medicine can seldom be solely directed at one target. When basic research identified tumor necrosis factor-alpha (TNF–α) as one of the key cytokines involved in several chronic inflammatory diseases with unknown causes, such as rheumatoid arthritis and Crohn's disease, it seemed logical to interfere with its action as a therapeutic strategy. While blocking cytokines may lead to dramatic clinical responses, it was perhaps naive to assume that there would be no adverse consequences. TNF–α plays a central role in the formation of granulomata, a major defence mechanism in the containment of mycobacterial disease and dimorphic fungi. Further, TNF–α increases the phagocytic ability of macrophages, enhancing intracellular killing of organisms in the presence of interferon gamma. Several TNF–α antagonists are now available and are increasingly being used in the treatment of rheumatoid arthritis, including infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira). Unfortunately, infectious complications associated with these drugs surfaced only as a result of postmarketing surveillance. Tuberculosis (TB) was responsible for the largest numbers of infections, with rates of 239 per 100 000 patients who have received infliximab and 74 per 100 000 in those treated with etanercept. Disease tended to occur near the beginning of treatment, 72% within 90 days with infliximab, but spread more evenly with entanercept with 28% occurring within the first 90 days. This suggests the mechanism is reactivation of latent tuberculous infection. Numerous other infections have also been reported, including listeriosis, nocardiosis, coccidiomycosis, histoplasmosis, cryptococcal disease, and disseminated nontuberculous mycobacteriosis. As many patients may be taking concurrent immunosuppressive agents it is possible the effects of TNF–α inhibitors are additive if not synergistic.

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While pulmonary TB is the most common manifestation of reactivation, both extra-pulmonary and disseminated tuberculosis have more commonly been reported with these medications and we have encountered a case of spinal TB. Clearly, prior to initiation of TNF–α inhibitors, a TB risk assessment is mandatory, including enquiry as to birth in high TB prevalence countries, previous tuberculosis exposures, PPD skin test reactivity, a chest X-ray for evidence of latent infection and to exclude active TB, and the performance of a skin test if not previously documented. Active cases require a full course of treatment prior to initiation of these medications. Screening for tuberculosis, however, presents its own challenges as rheumatoid lung disease may resemble TB on imaging, and ileocecal TB can be mistaken for Crohn's disease. Many cases of rheumatoid arthritis are on other immunosuppressive agents that may interfere with interpretation of the PPD skin test. The newer whole blood assays that measure the release of interferon gamma in vitro (QuantiFERON and T-spot TB test) may prove superior in this setting and are currently under evaluation. A PPD reaction of greater than 5 mm is considered positive in this setting. It is likely that TNF–α inhibition itself will interfere with the PPD reactivity, leading to false positives, and it has been reported in a limited number of patients tested serially.

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The agents are being used with increasing frequency as their value in other diseases such as ankylosing spondylitis, psoriatic arthrititis, and uveitis is documented, so an increasing number of patients will be at risk. At least for TB we have the ability to make these liaisons less dangerous.

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