EDITORIAL

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Patients treated with a tumor necrosis factor-α inhibitor are more likely to develop extrapulmonary tuberculosis

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See Article on Page 174-179

Tumor necrosis factor (TNF) and TNF receptors play a key role in mediating immune responses in acute and chronic inflammation. Over the past decade, TNF inhibitors have become invaluable in the treatment of chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and inflammatory bowel disease [1]. The United States Food and Drug Administration (FDA) approved infliximab, a humanized monoclonal antibody against TNF-α, for use in patients with Crohn's disease in 1998, and in those with rheumatoid arthritis in 1999. Although only one case of tuberculosis after infliximab therapy was reported in a clinical trial [2], 70 cases were detected through the MedWatch spontaneous reporting system of the FDA within 3 years of approval [3]. Subsequent studies revealed that the relative risk for tuberculosis is increased 1.6 to 25.1 times following TNF-α inhibitor therapy, depending on the clinical setting and the TNF-α inhibitor used [1]. Therefore, recent guidelines recommend that all patients undergoing TNF-α inhibitor therapy should be screened for tuberculosis, and that patients with latent tuberculosis infection (LTBI) receive preventive chemotherapy [1].

The role of TNF-α in the human immune response to tuberculosis remains unclear. Antibodies against TNF-α caused a reactivation of tuberculosis in a mouse model of LTBI [4]. TNF-α inhibitors have been used in South Korea since 2001. Screening and preventive chemotherapy for LTBI would seem to be essential before commencing TNF-α inhibitor therapy in South Korea, a country with an intermediate tuberculosis burden. Seong et al. [5] reported that the risk of tuberculosis is 9-fold higher in Korean patients with rheumatoid arthritis and 30-fold higher in rheumatoid arthritis patients treated with infliximab, compared with the general Korean population [5]. In this report, only 193 patients treated with TNF-α inhibitors were identified, two of whom developed tuberc ulosis during the study period [5]. In the current issue of *The Korean Journal of Internal Medicine*, Chung et al. [6] described the clinical characteristics and treatment responses of seven patients with tuberculosis among 457 treated with a TNF-α inhibitor. The incidences of tuberculosis after TNF-α inhibitor therapy were not significantly differ-

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ent between the reports of Seong et al. [5] and Chung et al. [6] (2/193, 1.0% [95% confidence interval (CI), 0.04% to 3.9%] vs. 7/457, 1.5% [95% CI, 0.7% to 3.2%]).

According to an official report of the Korean National Tuberculosis Association (http://www.knta.or.kr), the proportion of extrapulmonary tuberculosis among newly reported cases in Korea is less than 24%. Extrapulmonary involvement was common (57%) among TNF-α inhibitor users who developed tuberculosis according to Chung et al. [6]. This finding is comparable with the results of previous studies which included TNF-α inhibitor users [3] and solid organ transplant recipients [7,8]. In data from the FDA reporting system, the majority of the patients (56%) had extrapulmonary tuberculosis, and 24% had disseminated disease [3]. These patterns are similar to those of solid organ transplant recipients. Among kidney and liver transplant recipients who developed tuberculosis, extrapulmonary involvement was common (67%), including cases of disseminated disease (27% to 31%) [7,8]. Furthermore, classic symptoms of tuberculosis, such as fever, night sweats, and weight loss, may not be present [3,7]. This unusual manifestation of tuberculosis may make diagnosis uncertain. Therefore, the diagnosis of tuberculosis requires a high index of suspicion in patients treated with TNF-α inhibitors. Diagnostic invasive procedures such as tissue biopsy or aspiration of body fluids and abscesses are often required.

In the report by Chung et al. [6], most patients were not screened for LTBI, because the study was performed before the publication of official Korean guidelines for TNF-α inhibitor users. To diagnose LTBI, all patients undergoing TNF-α inhibitor therapy should be screened for a history of untreated or inadequately treated tuberculosis, and/or for recent contact with an active tuberculosis patient. In addition to the patient history, a tuberculin skin test must be included in LTBI screening. The prevalence of LTBI, determined by a tuberculin skin test (diameter of induration, > 10 mm), is estimated to be 37% in Korean patients treated with TNF-α inhibitors [9]. The ability of the tuberculin skin test to diagnose LTBI in patients with rheumatologic disease might be suboptimal, due to anergy to skin test antigens and to the effects of immunosuppressive drugs [9]. These shortcomings of tuberculin skin tests have generated interest in interferon-γ release assays [10]. However, further studies are awaited to determine whether the ability of interferon-γ release assays for LTBI can better predict the development of tuberculosis in TNF-α inhibitor users.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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