

Should Patients Under Long-term Anti-TNF Therapies be Followed for Tuberculosis Contamination?

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To the Editor:

Inhibiting tumor necrosis factor alpha (TNF α) has emerged as an effective therapy in inflammatory bowel diseases (IBDs)¹ but an increased risk to develop reactivation of latent tuberculosis (TB) was observed soon after its introduction.^{2,3} Hence, exclusion of active TB and treatment of latent tuberculosis infection (LTBI) have become clinically imperative prior to starting anti-TNF treatment. Patients should be screened for prior TB exposure. Chest radiograph must be performed for active TB detection.⁴ Several guidelines have suggested a tuberculin skin test (TST) prior to anti-TNF therapy but a high risk of anergy is observed due to the use of immunosuppressive drugs. T-cell interferon gamma release assays (IGRAs) are more sensitive and more specific than TST and could become an alternative for detection of LTBI.^{5,6} After starting the anti-TNF therapy in patients with negative TST, no data are available concerning the risk of developing new TB infection under anti-TNF treatment. In our daily practice we observed 2 cases of TST positivity after more than 1 year of anti-TNF therapy.

The first case concerned a 34-year-old male suffering from Crohn's disease (CD) treated with azathioprine for 1 year. A bitherapy with azathioprine and anti-TNF was then started. Prior to the infliximab therapy, clinical examination, chest x-ray, and TST using 5 units of tuberculin were normal. The patient had no history of TB exposure. The infliximab therapy was stopped after 4 years due to a loss of efficacy. Before switching to adalimumab treatment, the chest x-ray was normal. The patient, working as a prison guard, revealed a contact 6 months earlier with a prisoner suffering from active TB. TSTs performed every year at the prison were negative but it became strongly positive before starting adalimumab. The patient had neither clinical nor radiological signs of active TB suggesting a contamination by LTBI.

The second case was a 34-year-old female suffering from active ulcerative colitis (UC) despite corticosteroid and methotrexate therapy. Before infliximab treatment, the chest x-ray and the TST using 5 units of tuberculin were strictly negative. She had no history of TB exposure. The patient was treated with infliximab in monotherapy for 1 year. Because of a relapse 6 months later, adalimumab was proposed. At this time the chest x-ray and the clinical examination were normal. The patient had no history of recent TB exposure but she traveled recently to Rumania. The TST was repeated and revealed a large erythema and induration of 25 mm, suggesting a TB contamination without clinical or radiological signs of active TB.

One-third of the world's population has LTBI that can potentially progress to active disease in 5%-10% of the cases.^{7,8} The risk of developing clinical manifestations is greatly increased in the case of immunosuppression as with anti-TNF therapy but the rate is not exactly known. In the literature, all the cases of active TB occurring under anti-TNF therapy are described as the consequence of the reactivation of an LTBI already present before the treatment. No case of de novo active TB or LTBI is described either in human or in animal models.^{9,10} Our recent experience showed 2 TB contaminations in patients receiving long-term anti-TNF treatment. Despite its poor sensitivity in immunocompromised patients, the TST became highly positive in our 2 patients with a low risk of false positivity (no BCG vaccine, no endemic area for atypical mycobacterium). Moreover, the first had a well-documented contact with an infected prisoner and the second traveled in an endemic area for TB contamination. They had no clinical or radiologic sign of active TB suggesting the possibility of de novo LTBI. The rate of de novo LTBI under anti-TNF treatment and the risk of active TB are not documented. Screening anti-TNF treated patients for de novo LTBI by rigorous questioning, TST, or more sensitive tests like IGRAs could lead us to diagnose LTBI before active TB and to treat them effectively. These 2 cases highlight the risk of de novo TB contamination in anti-TNF-treated patients and question the optimal follow-up strategy of these patients.

REFERENCES

1. Maini SR. Infliximab treatment of rheumatoid arthritis. *Rheum Dis Clinics N Am.* 2004;30:329-347.
2. Keane J, Geeshon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med.* 2001;345:1098-1104.
3. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious disease associated with tumor necrosis factor antagonists. *Clin Infect Dis.* 2004;38:1261-1265.
4. Salmon-Ceron D. Recommendations for the prevention and management of in patients taking infliximab. *Ann Med Interne (Paris).* 2002;153:429-431.
5. Chapman AL, Munkanta M, Wilkinson KA, et al. Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of Mycobacterium tuberculosis-specific T cells. *AIDS.* 2002;16: 2285-2293.
6. Tarn LS, Li EK, Wong SM, et al. Risk factors and clinical features for tuberculosis among patients with systemic lupus erythematosus in Hong Kong. *Scand J Rheumatol.* 2002;31:296-300.
7. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med.* 2004;350:2060-2067.
8. Radhakrishna S, Frieden TR, Subramani R. Association of initial tuberculin sensitivity, age and sex with the incidence of tuberculosis in south India: a 15-year year follow-up. *Int J Tuberc Lung Dis.* 2003;7:1083-1091.
9. Flynn JL, Goldstein MM, Chan J, et al. Tumor necrosis factor-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice. *Immunity.* 1995;2:561-572.
10. Jacobs M, Samarina A, Grivennikov S, et al. Reactivation of tuberculosis by tumor necrosis factor neutralization. *Eur Cytokine Netw.* 2007;18:5-13.