Tumor Necrosis Factor-α Blocker Induced Tuberculosis

To the Editor

Patients who are treated with anti-tumor necrosis factor-α (anti-TNF-α) blockers are at risk of reactivation of latent tuberculosis (TB) infection (LTBI). The study by Dr. Malaviya, *et al* describes an approach to the diagnosis of LTBI prior to anti-TNF-α therapy[1]. Screening tests they advise are tuberculin skin test (TST), interferon-γ release assay, or Quantiferon TB Gold (QTB Gold), chest radiograph (CXR), and computed tomogram (CT) of the thorax. We describe 2 patients who developed active TB while taking infliximab, despite the recommended screening tests being negative.

Case 1: In March 2009, A 30-year-old male, with long standing ankylosing spondylitis (AS), complained of worsening of axial symptoms in spite of adequate nonsteroidal antiinflammatory drugs (NSAID). As the AS was active, infliximab therapy was offered. Baseline laboratory findings were: hemoglobin: 9.5 g/dl, leukocyte count: 10,012 cells/mm^3, erythrocyte sedimentation rate (ESR) 45 mm/h, platelets: 416,000/mm^3, serum glutamic pyruvic transaminase 22 IU/l, and serum creatinine 0.8 mg/dl. The LTBI screen tests including CXR, TST, and QTB Gold test were negative. CT thorax was not done. He was given 2 doses of infliximab (3 mg/kg per dose) 5 months apart. Three weeks after the second dose he developed a low grade fever and cough. There were scattered crackles on auscultation and the CXR showed consolidation in the right upper and middle zones. Although three sputum acid-fast bacilli (AFB) smears and AFB culture were negative, anti-TB therapy (ATT) was started on clinical grounds. The patient showed clinical and radiological resolution in 6 weeks' time.

Case 2: In March 2008, a 13-year-old boy was diagnosed to have Juvenile AS with peripheral arthritis. He improved with NSAID over 4 weeks. Six months later the AS relapsed and was refractory to NSAID and methotrexate. Laboratory reports were: hemoglobin: 10.7 g/dl, leukocyte count: 10,700 cells/cm^3, platelets: 430,000 cells/cm^3, ESR: 100 mm/h, and CXR: normal; TST and QTB Gold were both negative. Infliximab (3 mg/kg) was given June 5. In September 2009, he developed low grade fever, loss of appetite, and dry cough of 2 week duration. CXR showed right sided pleural effusion, aspiration of which revealed a lymphocytic predominant exudate with elevated adenosine deaminase level (156 iu), consistent with TB pleural effusion. ATT was initiated and he is now improving.

It is important to recognize and treat LTBI prior to institution of anti-TNF-α therapy. In both our patients, an attempt was made to exclude LTBI using the screen recommended by Malaviya, *et al*. As both patients initially showed no clinical evidence of TB, with a negative CXR, TST, and TB gold tests, a CT of the chest was not done. Despite having a negative screen, both our patients developed active TB after initiation of infliximab therapy.

False negative TST as a result of immune suppression can result in a false negative screen for LTBI. Park, *et al* showed that, of 86 patients who received anti-TNF-α therapy with a negative TST at the baseline[2], TST (repeated annually) converted to positive after a median interval of 33.3 months in 32.6% of patients. Interferon-γ release assay (IGRA) testing was found to have a 68.6% concordance with TST. Hence, combined testing with TST and IGRA can to an extent overcome the false negative TST.

We recently reported that by T cell specific ELISPOT (T spot) assay, the prevalence of LTBI in healthy, urban Indians is around 80%[3]. Unlike the TST, this is a specific assay for *Mycobacterium tuberculosis*, not confounded by previous bacillus Calmette Guerin BCG vaccination, or infection with environmental mycobacteria. The T-spot TB assay also has a lower likelihood of being rendered false negative by prednisolone therapy versus TST. This test could help identify LTBI in patients who are TST and IGRA negative.

In endemic regions like India, a new TB infection may be misclassified as a TB flare. Further, ELISPOT test, the TST and TB gold test, fail to differentiate between latent and active TB. This distinction is crucial, in order to choose between initiation of anti-TB prophylaxis or that of full-fledged ATT[4]. Since a normal chest radiograph does not rule out LTBI or active TB, correlation of IGRA and TST with clinical likelihood of LTBI is important[5]. This is especially true in India, where a CT chest cannot always be done due to cost constraints.

In conclusion, not even a battery of tests can completely exclude LTBI. Hence, even with a negative screen, the possibility of TB flare, or development of new TB infection, must always be kept in mind while initiating anti-TNF therapy. In such patients, combination of TST and IGRA, with regular repetition of these tests, will increase the likelihood of diagnosis of LTBI. It is also recommended that LTBI prophylaxis be continued in those patients receiving anti-TNF-α therapy who have been treated for TB disease prior to initiation of the same.

PRIYANKA KHARBANDA, MD; RUCHA DAGAONKAR, CANCHI BALAKRISHNAN, MD; ZARIR F. UDWADIA, MD, FRCP; Rheumatology and Pulmonology Units, PD Hinduja Hospital, Mumbai, India.

REFERENCES

1. Malaviya AN, Kapoor S, Garg S, Rawat R, Shankar S, Nagpal S, et al. Preventing TB flare in patients with inflammatory Rheumatic diseases receiving Tumor Necrosis Factor alpha (TNF alpha) inhibitors in India — an audit report. J Rheumatol 2009;36:1414-20.
2. Chung SJ, Kim JK, Park MC, Park YB, Lee SK. Positive conversion of tuberculin skin test and performance of interferon release assay to detect hidden tuberculosis infection during anti-tumor necrosis factor agent trial. J Rheumatol 2009;36:2416-20.
3. Lalvani A, Nagvenkar P, Udwadia Z, Pathan AA, Wilkinson KA, Shastri JS, et al. Enumeration of T cells specific for RD1- encoded antigens suggests a high prevalence of latent mycobacterium tuberculosis infection in healthy urban Indians. J Infect Dis 2001;183:469–77.
4. Winthrop KL, Chiller T. Preventing and treating biologic-associated opportunistic infections. Nat Rev Rheumatol 2009;5:405-10.
5. Martin J, Walsh C, Gibbs A, McDonnell T, Fearon U, Keane J, et al. Comparison of interferon {gamma} release assays and conventional screening tests before tumour necrosis factor {alpha} blockade in patients with inflammatory arthritis. Ann Rheum Dis 2010;69:181-5.

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