Does anti-tumour necrosis factor α treatment modify the tuberculin PPD response?

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Tumour necrosis factor α (TNF α) has a key role in chronic arthritis,¹ but it also participates in the defence against infection. TNF α , together with interferon γ , contributes to the immune response against mycobacteria.² This can explain the higher incidence of tuberculosis seen in patients receiving anti-TNF α treatment.³ Therefore, a tuberculin purified protein derivative (PPD) test has been recommended before starting anti-TNF α treatment to better identify patients at risk for tuberculosis reactivation requiring isoniazid treatment.⁴ However, patients with chronic arthritis can be anergic to delayed-type hypersensitivity (DTH) tests, owing to either active disease or to immunosuppressive treatment.⁵ Some authors have previously shown that the DTH response in patients given second line treatment improves, but the effect of anti-TNF α treatment is not known.⁶

We have studied, on the one hand, whether treatment with the anti-TNF α agent infliximab interferes with the cellular response to mycobacterial antigens involved in the tuberculin PPD test, decreasing the diagnostic value of the test, or whether, on the other hand, it can improve the anergic status of patients with active arthritis, leading to further reconsideration of latent tuberculosis treatment.

A prospective study was performed in 61 patients treated with infliximab because of active polyarthritis due to rheumatoid arthritis (43), psoriatic arthritis (3) or ankylosing spondylitis (15). A PPD skin test and thorax radiography were performed before the administration of infliximab to identify patients with latent tuberculosis at risk for active infection, and the PPD test was repeated after 54 weeks of treatment. Patients received nine infusions of 3–5 mg/kg infliximab (at weeks 0, 2, 6, and then every 8 weeks). RT-23 tuberculin PPD (2 U) was intradermally injected in the forearm and the response examined 72 hours later. More than 5 mm of induration was considered positive and in this case, 9 months isoniazid was indicated as treatment of the latent infection.

The mean (SD) age of the patients was 47 (13) years and mean (SD) disease duration 12 (8) years. At the first PPD test, 55 patients were receiving methotrexate, two sulfasalazine, three azathioprine, and one leflunomide. All patients were receiving low dose steroids (<10 mg prednisone). Forty eight patients were PPD negative and 13 positive, and all of them lacked tuberculosis radiological features. After 54 weeks, the initial PPD result of four patients changed. Three patients initially negative were positive in the second test. At the second test these three patients had complete remission of their disease (rheumatoid arthritis in two cases and ankylosing spondylitis in the other). In none of these patients, was a tuberculosis contact identified, and after 1 year of follow up, clinical, radiological or microbiological data consistent with mycobacterium infection have not been detected. This change led to the indication of isoniazid prophylaxis in these patients according to current

recommendations for anti-TNF α treatment.⁴ The other patient had an initially positive PPD test due to pulmonary tuberculosis diagnosed and treated 20 years before that became negative after infliximab treatment. In the patients with an initially positive PPD, the mean (SD) induration diameter increased from 12 (7) to 16 (7) mm after infliximab treatment ($p = 0.024$).

The nature of the deleterious effect of TNF α neutralisation in the defence against mycobacterial infection in humans remains controversial. In TNF α deficient mice, mycobacterial infection is characterised by stronger CD4 responses to mycobacterial antigens, leading to enhanced tissular necrosis.⁷ Our observations are consistent with the idea that TNF α neutralisation does not interfere with the cellular immune response to mycobacterial antigens, because it does not abrogate the DTH response involved in the PPD reaction. Contrarily, anti-TNF α treatment can improve the diagnostic value of the test by improving the anergic status associated with active arthritis, and this has important therapeutic implications. According to the reported observations, in patients with negative PPD responses who are receiving anti-TNF α inhibitors, repeat PPD testing is recommended to improve the identification of patients requiring isoniazid treatment.

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REFERENCES

1. **Felmann M**, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. *Annu Rev Immunol* 1996;**14**:397–440.
2. **Flynn JL**, Goldstein MM, Chan J, Triebold KJ, Pfler K, Lowenstein R, *et al*. TNF-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice. *Immunity* 1995;**2**:561–72.
3. **Gómez-Reino JJ**, Carmona L, Valverde VR, Mola EM, Montero M, BIOBADASER Group. Treatment of rheumatoid arthritis with TNF inhibitors may predispose to significant increase in tuberculosis, a multicenter active-surveillance report. *Arthritis Rheum* 2003;**48**:2085–91.
4. **Furst DE**, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Dougados M, *et al*. Updated consensus statement on biological agents for treatment of rheumatoid arthritis and other immune mediated inflammatory diseases (May 2003). *Ann Rheum Dis* 2003;**62**(suppl II):ii2–9.
5. **Helliwell MG**, Panayi GS, Unger A. Delayed cutaneous hypersensitivity in rheumatoid arthritis: the influence of nutrition and drug therapy. *Clin Rheumatol* 1984;**3**:39–45.
6. **Smith MD**, Smith A, O'Donnell J, Ahern MJ, Roberts-Thomson PJ. Impaired delayed-type cutaneous hypersensitivity in rheumatoid arthritis reversed by chrysotherapy. *Ann Rheum Dis* 1989;**48**:108–13.
7. **Zganiacz A**, Santosuosso M, Wang J, Yang T, Chen L, Anzulovic M, *et al*. TNF-alpha is a critical negative regulator of type 1 immune activation during intracellular bacterial infection. *J Clin Invest* 2004;**113**:401–13.