TB screening and anti-TNFα treatment

We read with interest the letter by Provenzano *et al*[1] on TB screening and anti-TNFα treatment and wish to comment on this highly topical subject.

Latent TB infection (LTBI) was diagnosed in 24.6% of the 69 rheumatological patients undergoing evaluation for anti-TNFα treatment (n = 17), six of whom received anti-TNFα treatment and TB chemoprophylaxis. The ethnicity and place of birth was not given, which may have had some bearing on this apparently high incidence of LTBI. Previous BCG vaccination was not reported in the cohort, particularly in those (8.7%) with a positive Mantoux test, which could give rise to false positive results. Before Mantoux testing steroids were stopped (for 1 week) but no comment is made regarding other immunosuppressive treatments which might interfere with the accuracy of tuberculin skin testing[2] and would account for the poor sensitivity of the Mantoux test in this cohort (sensitivity 35%). It is also unclear whether the two patients with a previous history of TB had received appropriate treatment at the time of initial diagnosis or whether they were subsequently included in the six patients who received chemoprophylaxis. Recent BTS guidelines recommend that patients who have previously been adequately treated should be monitored rather than receive chemoprophylaxis.[2] Four of the six patients who received isoniazid chemoprophylaxis were required to stop the drug due to hepatotoxicity. The authors did not comment on whether these patients had abnormal liver function tests before receiving isoniazid, nor on the degree of hepatotoxicity required to discontinue the drug.

Our experience is with similarly small numbers. Nine out of 50 (18%) rheumatological patients screened for anti-TNFα treatment were referred to our TB clinic after they were found to have either risk factors for TB (ethnicity and place of birth, n = 7), positive TB skin tests after recent TB exposure (n = 1), or a history of previous adequately treated TB (n = 1). Our patients had a mean age of 55 years, identical to that reported by Provenzano *et al*, although they did not report whether the mean age of those receiving isoniazid was similar to that of the entire cohort. All nine of our patients were on immunosuppressive therapy including steroid therapy at the time of screening. One patient had abnormal liver function tests thought to be secondary to methotrexate, so TB chemoprophylaxis has been deferred in this patient and methotrexate has been withdrawn awaiting normalisation of liver function tests. Six patients with normal liver function tests have commenced 6 months of treatment with isoniazid before starting anti-TNFα treatment after a risk assessment according to BTS guidelines. One patient with rheumatoid arthritis receiving hydroxychloroquine and prednisolone developed an isolated raised ALT (>200) with no symptoms and isoniazid was discontinued in accordance with previously published recommendations.[3]

While these numbers are small, they suggest that the high level of hepatotoxicity reported by Provenzano *et al* is not universal. We agree that the additive effects of concurrent therapy for active rheumatological disease and rheumatological disease per se might increase the rates of liver toxicity in patients treated with TB chemoprophylaxis. We suggest that further studies are needed in this patient population to assess whether the incidence of significant hepatotoxicity related to TB chemoprophylaxis is associated with identifiable risk factors such as age, ethnicity, co-morbidity, or medications such as immunosuppressive therapy. In addition, further research is required to determine the value of interferon γ assays for the diagnosis of LTBI in this patient population, given the limitations of TB skin tests and risk assessments.

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Author's reply

I thank Dr Creer and colleagues for their interest in our letter[1] and welcome the opportunity to characterise our patients better and to make some additional comments.

All of the 69 rheumatological patients that we screened for TB infection were white, born in Italy, and none had previously received BCG vaccination. The high prevalence of latent TB (24.6%) was predominantly due to the frequent observation of radiographic lesions consistent with this diagnosis (20.3%). The radiologist had been specifically asked to look for this kind of lesion, and this probably enhanced the sensitivity of its evaluation compared with a "blind" routine observation. However, it must be stressed that there were radiographic abnormalities consistent with previous TB that are rather non-specific such as pleural scarring. This confirms the need for an evaluation on an individualised basis, and the recently published BTS recommendations[2] are very helpful to the clinician managing this highly topical subject.

I agree that interpretation of the Mantoux test can be very misleading in this group of patients. In our 69 patients, although we stopped steroids and all immunosuppressive agents at least 1 week before performing the Mantoux test, this action did not preclude a significant chance of false negatives. Furthermore, the BTS guidelines stress the importance of ethnicity and place of birth in assessing the annual risk of TB and the need to take into account the risks of chemoprophylaxis before starting it. We observed a very high level of hepatotoxicity in our patients receiving chemoprophylaxis: we had to discontinue isoniazid in four of the six patients due to increased levels of AST (grade 3) and/or ALT (grade 4). All of these patients had normal AST/ALT levels before starting chemoprophylaxis and were seronegative for HBSAg and anti-HCV. Their mean age was 58.2 years (range 54–65). We are conscious that this high rate of hepatotoxicity may not be universal, but it is interesting that all of our six patients who received chemoprophylaxis according to the Italian guidelines should not be treated according to the more recent BTS recommendations.

It has already been shown that the application of specific guidelines has led to a significant reduction in the number of cases of TB in patients receiving anti-TNFα treatment.[3] We believe that the BTS guidelines, which try to quantify the risks of TB reactivation in the single patient, will prove useful in avoiding overuse of chemoprophylaxis. There is only one point that we want to make concerning these guidelines: in clinical practice it is very hard to justify a 6 month delay in starting anti-TNFα treatment in patients needing chemoprophylaxis.

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High *Pseudomonas aeruginosa* acquisition rate in CF

Chronic colonisation of the lungs with *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) is associated with reduced lung function and life expectancy. Prevention of chronic colonisation might be achieved by avoidance of, or early and aggressive treatment of, primary *P aeruginosa* acquisition.[1] Segregation of uninfected indivduals from chronically *P aeruginosa* colonised CF patients is advocated to prevent cross infection.[2] As surveillance studies suggest that the airways of healthy children are rarely colonised with *P aeruginosa*,[3] healthy individuals are not regarded as a potential source of *P aeruginosa* acquisition. In addition, it has been shown that acquisition of *P aeruginosa* in CF patients is often preceded by a viral respiratory infection.[4] We hypothesised that the incidence of *P aeruginosa* acquisition during periods of acute respiratory infections (ARI) is equal in both healthy and CF individuals, and considerably exceeds the prevalence in asymptomatic children shown in surveillance studies.

We performed systematic oropharyngeal cultures during periods of ARI between November and May in 20 young children with CF of mean (SD) age 3.6 (2.0) years (range 0.1–7.4) and 19 unrelated age matched healthy controls of mean (SD) age 3.6 (1.7) years. All children were negative for *P aeruginosa* at the start of the study. Subjects were contacted twice a week with a standard questionnaire regarding symptoms of ARI. If any symptom was present a physician performed an oropharyngeal culture. Cultures