TB screening and anti-TNFα treatment

We read with interest the letter by Provenzano et al. 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 chemophrophylaxis. The ethnicity and place of birth was not given in which we 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 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 chemophrophylaxis. Recent BTS guidelines recommend that patients who have previously been adequately treated should be monitored rather than receive chemophrophylaxis. Four of the six patients who received isoniazid chemophrophylaxis 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 test (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 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 chemophrophylaxis 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.

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 concomitant medication for active rheumatological disease and rheumatological disease per se might increase the rates of liver toxicity in patients treated with TB chemophrophylaxis. We suggest that further studies are needed in this patient population to assess whether the incidence of significant hepatotoxicity related to TB chemophrophylaxis 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 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 are very helpful to the clinician managing this highly topical subject.

I agree that interpretation of the Mantoux test can be very challenging 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 number 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 chemophrophylaxis before deciding to commence chemophrophylaxis: 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 chemophrophylaxis 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 chemophrophylaxis 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. 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 chemophrophylaxis. 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 chemophrophylaxis.

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References


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. Segregation of infected individuals from chromically P aeruginosa colonised patients is advocated to prevent cross infection. As surveillance studies suggest that the airways of healthy children are rarely colonised with P aeruginosa, 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. We hypothesised that the incidence of P aeruginosa colonisation in young patients treated with inhaled corticosteroids for asthma is high and that routine screening for 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 and any symptom was present a physician performed an oropharyngeal culture. Cultures were performed every 7 days during periods of ARI and every 14 days during periods of stable health. A mean of 2.5 samples were collected in each patient during each ARI period. ARI episodes were defined as episodes of symptoms of ARI with a positive viral culture and a multipathogen culture on a 14 day interval. Positive cultures of P aeruginosa were confirmed by colony typing. At the end of each study period, P aeruginosa genomic DNA was extracted from culture positive ARI samples, using a QIAamp DNA Mini Kit, according to the manufacturer’s instructions.

Phylogenetic analysis

P aeruginosa isolates were genotyped using a nested polymerase chain reaction (PCR) for the oprB-glaA intergenic region and a multiplex PCR for the oprM-glaG intergenic region. The two enzyme fragment length polymorphisms (EFLP) were combined for each isolate to form a unique genotype. In the present study, 162 samples from CF patients and 45 samples from healthy controls were genotyped.

Results

A total of 25 CF patients had one or more episodes of P aeruginosa acquisition during the study period, with a mean of 1.9 episodes per patient. In 19 of these patients, the first episode of P aeruginosa acquisition occurred in the follow-up period. The mean number of ARI episodes during the follow-up period was 7.3 (range 1–24). The acquisition rate was 31 episodes per 100 person weeks, which is significantly higher than that observed in the healthy control group (0.7 episodes per 100 person weeks). The acquisition rate of P aeruginosa in CF patients was significantly higher than that observed in the healthy control group (0.7 episodes per 100 person weeks). The acquisition rate of P aeruginosa in CF patients was significantly higher than that observed in the healthy control group (0.7 episodes per 100 person weeks). The acquisition rate of P aeruginosa in CF patients was significantly higher than that observed in the healthy control group (0.7 episodes per 100 person weeks). The acquisition rate of P aeruginosa in CF patients was significantly higher than that observed in the healthy control group (0.7 episodes per 100 person weeks). The acquisition rate of P aeruginosa in CF patients was significantly higher than that observed in the healthy control group (0.7 episodes per 100 person weeks). The acquisition rate of P aeruginosa in CF patients was significantly higher than that observed in the healthy control group (0.7 episodes per 100 person weeks). The acquisition rate of P aeruginosa in CF patients was significantly higher than that observed in the healthy control group (0.7 episodes per 100 person weeks).
from CF patients were also taken at routine visits. The study was approved by the local ethics review committee and all parents of the children gave written informed consent. A mean (SD) number of 7.5 (2.7) (range 2–13) and 5.1 (1.8) (range 2–9) oropharyngeal cultures were taken from CF patients and healthy controls, respectively. During the study period six children with CF (30%) had at least one P. aeruginosa positive culture compared with seven (37%) healthy controls. Cultures following a positive culture in healthy children were always negative for P. aeruginosa, while in four of six (67%) CF children short term follow up cultures remained positive for P. aeruginosa and anti-pseudomonal treatment was started.

This study showed that P. aeruginosa acquisition frequently occurs in periods of ARI in both children with CF and healthy controls. While healthy individuals easily clear P. aeruginosa, most CF patients remain positive and require anti-pseudomonal treatment. In the present study we sampled during periods of ARI, which are highly related to respiratory viruses in otherwise healthy children. In line with former data in CF, these results suggest that respiratory viral infections facilitate P. aeruginosa acquisition and colonisation. The high prevalence of P. aeruginosa in the airways of healthy children during ARI is in contrast with earlier findings which suggest that P. aeruginosa colonisation rarely occurs in the airways of healthy individuals. Our data could suggest that even healthy individuals with ARI are a potential source for P. aeruginosa acquisition in CF patients. If confirmed, it could have major consequences for current segregation policies which simply avoid contacts between CF patients. It might imply limiting contacts between both CF and non-CF individuals in periods of ARI. Or should we conclude that prevention of P. aeruginosa acquisition is practically unrealis-

cic? Our data urge for studies on the relationship between respiratory viral infections and bacteria in CF, and on the transmission of P. aeruginosa between healthy individuals and CF patients. New insights might change current prevention rules and might open new approaches to effective prevention of P. aeruginosa acquisition in patients with CF. Prophylactic treatment with anti-pseudomonal antibiotics in periods of ARI might be an interesting option.

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TW has served as consultant for Pfizer and Abbott. JK has participated in unrestricted educational activities supported by Abbott for which speakers fees were received from 2002 to 2005 and co-investigator on a clinical trial endorsed by Abbott which was concluded in 2005; CvdE received research grants and speakers fees from GlaxoSmithKline. None of the other authors has any financial interest or financial relationships with a commercial entity that has an interest in the subject of this manuscript.

References

Association between sibship size and allergic diseases in the Glasgow Alumni Study

We read the interesting study by Kinra et al. which gives us important information on the relationship between sibship size, birth order, and allergic disease in British students born in the first half of the 20th century. There are, however, a few points which we would like to raise:

1. The authors observed a stronger association between sibship size and allergy in the oldest cohort and interpreted this finding as supporting the hygiene hypothesis because of a postulated larger difference in hygiene between larger and smaller families in this cohort compared with younger cohorts. However, another possible explanation—not related to the hygiene hypothesis—is the change of determinants of family size. With modernisation and emancipation of women related to the hygiene hypothesis — modernisation and emancipation of women related to the hygiene hypothesis — increasing popularity of condoms, all taking place in the first half of the 20th century, the determinants of family size may have shifted considerably during this period with probable consequences for the association between family size and allergy.

2. Similarly, an interaction between socioeconomic status (SES) and birth order was observed, and interpreted as supporting the hygiene finding. However, other explanations cannot be excluded if we assume a prenatal birth order effect: a stronger relationship between birth order and allergy in lower SES categories might be due to a possibly higher rate of spontaneous abortions in these groups, leading to differential underestimation of birth order (or, rather, number of pregnancies). This scenario would also explain the fact that such an interaction was not observed for sibship size.

3. In the comparison of the results with those of other studies, the authors point out that two “negative” studies were due to lack of power. Firstly, it should be noted that these studies were not negative. In the study by Jarvis et al. a significant negative association (adjusted for birth order and relevant determinants) between allergy and sibship size was found, while in our study the corresponding association with birth order was highly significant. Secondly, in our study the adjusted association with sibship size was indeed not significant (p value for trend 0.34), but the adjusted odds ratio (OR) for one extra sibling (allergy/no allergy) was positive (1.07) while its 95% confidence interval (95% CI) of 0.85 to 1.34 excluded any important negative trends (OR and 95% CI for trend not shown in paper).

4. The contents of table 2 are not in agreement with the title: the results for asthma and combined allergic diseases are not shown.

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Competing interests: none

Dr Kinra was asked to comment, but no reply was received by the time this issue of Thorax went to press.

References

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In the paper entitled “COPD exacerbations – 4 years later” by S Scott, P Walker and P M A Calverley which appeared in the May issue of Thorax (2006;61:440–7), the dose of tiotropium used in the studies by Casaburi and Brusasco referred to in table 1 on page 444 which currently reads “18 μg twice daily” should read “18 μg once daily”. The publishers apologise for this error.