after more than 10 yrs of disease. Although the assessments were not blinded, to the patient’s perception of the skin involvement, the relapses were confirmed by two different methods performed by three different examiners (ultrasound by M.W. and skin score by A.S. or A.A.), which add substance to the report. This case also suggests that azathioprine should be subjected to controlled trials in SSc.

Rheumatology key message

- Relapses of skin involvement in SSc may occur after several years and may be related to decrease or discontinuation of therapy.

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Comment on: Use of the QuantiFERON TB Gold test as part of a screening programme in patients with RA under consideration for treatment with anti-TNF-α agents: the Newcastle (UK) experience

Sir, we read with interest the recent article by Pratt et al. [1] on the use of QuantiFERON-TB® Gold test (QTG) as a part of the screening programme in patients with RA under consideration for treatment with anti-tumour necrosis factor (TNF-α) agents. They conclude that the use of QTG test in this group of patients is feasible, useful, cost-effective and unaffected by the impaired immunocompetence of the group. However, before QTG testing can be advocated as a screening tool in these circumstances, we feel there are a number of unanswered questions.

In 2001, the QTG test was approved by the Food and Drug Administration as an aid for detecting latent Mycobacterium tuberculosis infection (LTBI) [2, 3]. Limitations of QTG include the need to draw blood and process it within 12 h after collection, and the limited laboratory and clinical experience with the assay. The utility of QTG in predicting the progression to active tuberculosis has not been evaluated. The Centre for Disease Control guidelines on the use of QTG does not recommend its use for the screening of children aged <17 yrs, pregnant women, or for persons with clinical conditions that increase the risk for progression of LTBI to active tuberculosis (TB) (e.g. human immunodeficiency virus infection, those receiving immunosuppressing drugs, chronic renal disease, diabetes, etc.) [4]. It is currently recommended that the tuberculin skin test (TST) be employed in combination with a risk stratification strategy in these situations [5]. In other words, in the context of impaired immunocompetence, QTG faces the same limitations as TST. Since the cohort used in the study is identified as immunocompromised RA patients, this makes us wonder whether the negative QTG in 80% of the study population [1] were true negatives or those affected by poor T-cell response secondary to immunocompromise [6]. About 10% of LTBI cases will eventually progress to clinical TB infection, and therefore longer follow-up of the study cohort might provide useful data about the negative predictive value of this test.

Three out of the seven patients who had positive QTG did not receive treatment. This is not surprising and confirms earlier reports for the lack of the predictive value of positive blood test results for progression to TB [7]. Furthermore, many indeterminate test results seem to have compounded the picture rendering active decision making to no more than a qualified guess. The opportunity to compare the existing evaluation pathway with QTG analysis has not been provided by the authors, and it is therefore not possible to make an independent and informed observation about the added utility of QTG.

One of the potential advantages of QTG claimed over TST is that the studies have shown it being less affected by prior Bacille Calmette Guérin (BCG) vaccination [2]. However, a recent study on the risk factors for a positive TST clearly stated that having a BCG scar did not increase the risk of a positive skin test in unexposed individuals [8]. This again would question the cost-effectiveness in its use as a screening tool for TB exposure in low prevalence countries such as the UK.

We want to remind all readers that the TST is free of charge and all future tests should satisfy the health economic argument before being considered as an alternative screening tool, unless their superior specificity and predictive values would force a major shift in diagnostic and therapeutic pathways.

We believe that TST along with the risk stratification guidelines proposed by the British Thoracic Society [5] still remains an invaluable initial screening tool for LTBI in patients with RA. QTG test use, however, would probably be better restricted to a small group of patients with RA who have relatively short disease duration, who are on no or a small dose of steroids and are not at high risk of developing TB on ethnic or geographical grounds. Furthermore, studies to ascertain whether TST alone or in combination with the QTG test for screening of LTBI is cost-effective in reducing the disease burden of TB are awaited.

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4 Centers for Disease Control and Prevention. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5002a2.htm


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Comment on: Use of the Quantiferon-TB® Gold test as part of a screening programme in patients with RA under consideration for treatment with anti-TNF-α agents: the Newcastle (UK) experience: reply

Sir, We are grateful to Dr Kaushik and co-authors [1] for their cautious comments regarding the interpretation of data arising from our audit [2]. We agree wholeheartedly that further and more in-depth studies are needed in this area to properly establish the precise role of IFNγ-based tests in screening for Latent tuberculosis infection (LTBI) amongst RA patients due to start anti-TNF-α therapy, with a particular emphasis on cost-effectiveness (which, in our concluding remarks, we clearly stated was a matter of potential, not fact). However, we are of the opinion that the shortcomings of the Quantiferon®-TB® Gold test (QTG) summarized by Kaushik et al. [1] are surmountable, whereas some of those of the tuberculin skin test (TST)—in particular, its recognized lack of specificity amongst bacille Calmette-Guérin (BCG)-exposed individuals in low-prevalence populations [3]—are not. Kaushik et al. [1] contest the validity of this latter shortcoming, but we would question their reliance in this point on a study of an epidemiologically rather distinct population from Guinea-Bissau which addressed the separate issue of tuberculosis (TB) contact-tracing [4]. Furthermore, we feel that before describing the tuberculin skin test (TST) as ‘free’, the cost of professional time involved in its administration and interpretation over two patient visits should be taken into account. In accordance with the now familiar British Thoracic Society (BTS) guidelines [5], therefore, which conclude that the TST will be unhelpful in screening patients who have been on immunosuppressive therapy (including corticosteroids and methotrexate), we chose not to employ that test as a screening tool in our patient cohort. We would, however, highlight a recent report [6] that did make comparison between TST and QTG in predominately Caucasian patients with rheumatic conditions, in which prior BCG vaccination was shown to affect TST but not QTG outcome.

The risk stratification process, advocated for use in immunosuppressed patients by the BTS guidelines [5] and referred to by our correspondents, which balances an estimate for age- and ethnicity-adjusted annual risk of TB in anti-TNF-α-treated patients with the hepatic risks of chemoprophylaxis, was published some time after recruitment for our audit commenced. We are grateful for the opportunity to mention that when applied retrospectively, these criteria would have identified just one (female, Asian) patient in our cohort as warranting chemoprophylaxis; this patient was QTG-negative and had no complications after 1 yr of etanercept treatment. It is of course not possible to say with certainty whether any of the four patients ultimately treated with anti-TNF-α agents who had positive QTG tests, all of whom underwent respiratory physician-guided chemoprophylaxis, did indeed represent ‘true positives’ with respect to LTBI.

Dr Kaushik and co-authors [1] doubt that the QTG test has a robust negative predictive value in our RA patient population. Specifically, they wonder whether some of the 83% of patients who were QTG-negative might have simply mounted inadequate T-cell responses secondary to immunocompromise. In such a scenario, a given sample’s incubation with mitogen in a positive control reaction would, because of T-cell hyporesponsiveness, fail to induce IFNγ secretion above the threshold necessary for interpretability, and the test result would by definition be indeterminate rather than negative [7]. This particular mechanism for the derivation of false negatives is thus neatly circumvented, although it is true that others may not be. In the absence of a satisfactory gold standard LTBI test, assessment of the negative predictive value of the QTG test is therefore ultimately reliant on long-term follow-up, and although we feel that our follow-up period (average ~18 months) should have been sufficient in most cases (particularly amongst infliximab-treated patients in whom LTBI reactivations occur preferentially within 3 months of treatment initiation [8]), we concede that a longer period of follow-up amongst a larger population size would be desirable: this is of course an ongoing concern.

Kaushik et al. [1] object to the ‘many’ (10% of our cohort) individuals whose QTG test result was indeterminate and hence uninformative, and in whom a combination of careful history-taking (including TB contact exposure), clinical examination and radiological evaluation was the sole decision-making tool—a process referred to by our correspondents as qualified guesswork. We would draw attention to the considerably higher proportion (~72%) of our ‘immunocompromised’ patient population who were known to have had prior exposure to BCG, and in whom interpretation of a positive TST would have been difficult, and point out once again that our rate of QTG indeterminate test results is comparable with that seen in non-immunocompromised cohorts elsewhere [9], suggesting that the informativeness of this test in the clinical context described is not adversely affected by T-cell hyporesponsiveness, a finding corroborated independently (and perhaps yet more convincingly) by others [6].

We thank our correspondents once more for their constructive remarks, but stand by our assertion that use of the QTG test for this purpose is feasible, potentially cost-effective and not apparently affected by increased rates of uninformative results in our clinical setting.

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