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An evaluation of the use of a negative interferon-γ release assay for tuberculosis screening before TNF antagonist therapy

To the Editor:

Tumour necrosis factor (TNF)-α antagonists, such as infliximab, adalimumab and etanercept, are widely used to treat immune-mediated inflammatory diseases. These drugs increase the risk of latent infection with *Mycobacterium tuberculosis* (LTBI) reactivation [1, 2]. Tuberculosis (TB) preventative chemotherapy significantly reduces this risk (74%); hence, in the UK, patients are screened for LTBI before starting TNF antagonist therapy [3]. The optimum screening strategy remains unclear. Strategies include combinations of clinical risk stratification data, T-cell interferon-γ release assay (IGRA) tests and tuberculin skin tests (TSTs) [2, 4, 5]. These tests have limitations, and have discordant results when compared [6].

The 2005 British Thoracic Society (BTS) guidelines recommend the use of risk stratification tables based on population demographics. These balance the likelihood of LTBI with the risk of therapy-induced hepatotoxicity to guide preventative chemotherapy decisions [7].

Since 2005, IGRAs have become widely available and suggested as a TST alternative [8]. Guidelines have suggested that all IGRA-positive patients (unless secondary to previous, fully treated TB) be given preventative chemotherapy prior to commencing TNF antagonist therapy [9]. This generally consists of 6 months of isoniazid, or 3 months of rifampicin and isoniazid [10]. However, the management of IGRA-negative patients is more complex and this study focuses on this.

At our centre, patients with a negative IGRA (enzyme-linked immunospot assay) and normal chest radiography commence TNF antagonist therapy without referral for further LTBI risk assessment. This is

based on the improved performance of the IGRA in detecting LTBI compared with the TST, particularly in the context of other immunosuppressive drugs and previous bacille Calmette–Guérin vaccination [2, 11]. This policy is in line with some other centres [2, 12]. Others have suggested additional screening with risk stratification tables and/or TSTs given the possibility of false-negative IGRA results [13]. The aim of our study was to evaluate this reliance on a negative IGRA by assessing TB reactivation rates and cost savings of this screening approach.

We conducted a retrospective review of consecutive patients receiving infliximab, adalimumab or etanercept at Chelsea and Westminster Hospital (London, UK) between January 2008 and June 2013. Hospital pharmacy dispensing data identified patients and electronic patient records (EPRs) provided clinical data. Patients were contacted to ascertain any unavailable information regarding country of birth or year of UK entry. These demographic data were used to stratify patients retrospectively using BTS risk stratification tables, identifying those who would have been offered TB preventative chemotherapy [7].

The London TB Register was searched to identify active TB cases. This register is maintained by Public Health England, and includes data from all London clinics. Cost estimates were from hospital tariffs and the British National Formulary. The National Research Ethics Service confirmed this was a service evaluation.

544 patient episodes of infliximab, adalimumab or etanercept therapy were identified between January 1, 2008 and June 24, 2013. The ethnicity distribution was 70.7% Caucasian, 10.7% Asian, 6.6% African, 6.1% other, 2.9% mixed race, 0.7% Chinese and 2.3% unavailable. 71.1% were UK born, 15.8% born abroad and 13.1% unknown. 22.5% had Crohn's disease, 10.9% rheumatoid arthritis, 3.7% ulcerative colitis, 57.4% unknown, and the remainder had dermatological, inflammatory or vasculitic disorders. 11.7% received two or more TNF antagonists. The median (interquartile range) time from IGRA to TNF antagonist treatment was 85 (22–317) days and treatment to TB register review 2.43 (1.7–4.3) years.

The data are detailed in figure 1. All positive/indeterminate IGRA patients (n=26) were referred to the TB clinic for preventative chemotherapy prior to TNF antagonist therapy. 353 IGRA-negative patients were commenced on TNF antagonist therapy without further LTBI assessment. Of these, 184 (91.5%) out of 201 were taking other immunosuppressive medications (of available data). One patient had HIV. There were 165 unavailable IGRA results.

Had all IGRA-negative patients been formally risk stratified before TNF antagonist therapy, 353 clinic appointments (£241 per patient) would have been required. A minimum of 41 (as this is based on ethnicity data of only 335 cases) would have been prescribed preventative chemotherapy, necessitating three further appointments minimum (£396 per patient) and a chemotherapy course (£82.50 per 6 months of isoniazid). This would cost around £101 647.50 over 5.5 years, based on Chelsea and Westminster Hospital National Health Service tariffs and the British National Formulary. This is an underestimate, as it excludes all unavailable IGRA patients (518 appointments, £149 720 if included in the calculation) and those without available ethnicity data.

Searching the London TB Register revealed one patient diagnosed with active TB 6 months after commencing adalimumab. This patient was IGRA-negative and would have been offered preventative chemotherapy based on risk table stratification.

A recent UK study evaluated a triple testing approach to identify TB preventative chemotherapy requirement in rheumatological patients requiring TNF antagonist therapy [13]. An increased yield of patients was identified as requiring preventative chemotherapy using BTS risk stratification, an IGRA and a TST than with any method alone. This intensive approach may further reduce the LTBI burden in line with TB elimination strategies [14]. However, there is no gold standard for the diagnosis of LTBI and it is not possible to evaluate prognostic values of this approach. Risk assessment screening involves significant time, resources and cost, with those prescribed preventative chemotherapy being at risk of hepatotoxicity [7]. The approach in this study suggests a negative IGRA is a good screening test. This is a pragmatic approach, and an awareness of the limitations and understanding that results may not be transferable to all patients and populations is important.

A further recent UK study evaluated the outcomes of 125 inflammatory bowel disease patients using a similar pragmatic screening approach [12]. Our study adds to these findings with a significantly larger population encompassing numerous inflammatory conditions, longer follow-up and use of the London TB Register to assess TB reactivation. In addition, individual BTS risk table calculations were performed by contacting patients for accurate demographic data.

Some information regarding concurrent immunosuppression was unavailable. Possibly, data were more readily available when patients were on immunosuppression; therefore, our figure of 91.5% taking other

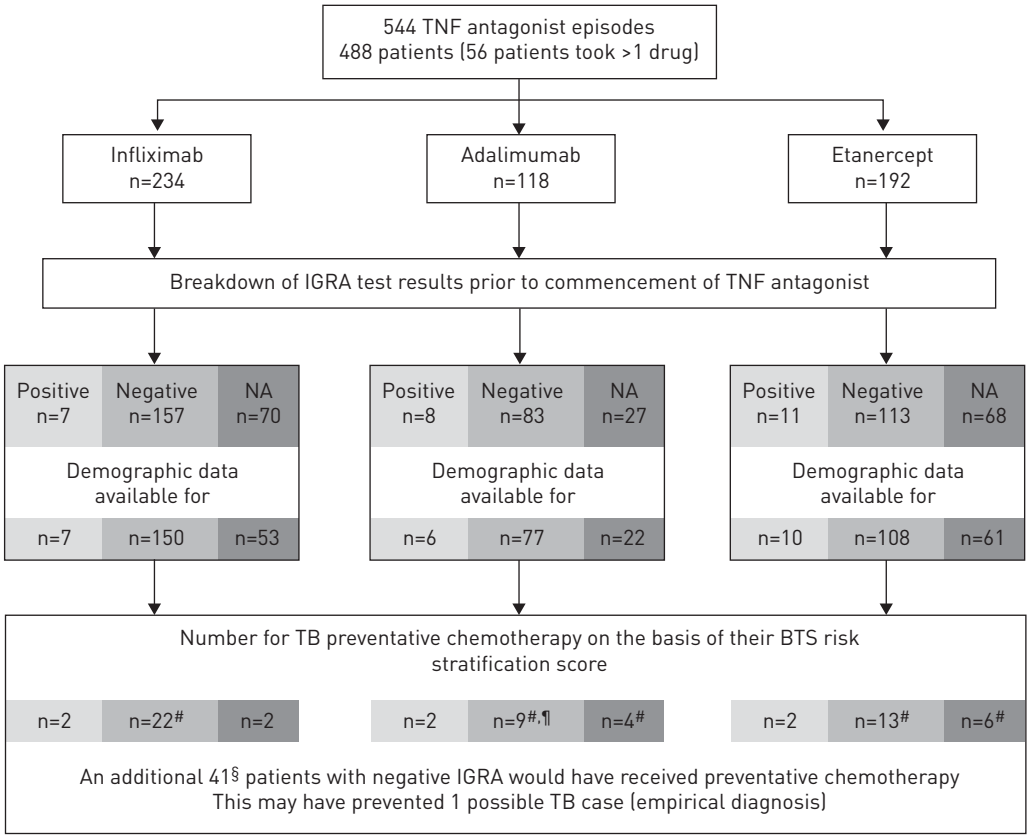

FIGURE 1 Patients who received tumour necrosis factor (TNF) antagonists during the period from January 1, 2008 to June 24, 2013. IGRA: interferon-γ release assay; NA: not available; TB: tuberculosis; BTS: British Thoracic Society. #: a total of four patients received two different TNF antagonists and, hence, the additional patient number is calculated taking this into account; ¶: this group contained the one patient who subsequently developed TB (empirical diagnosis); §: an additional 52# patients with negative/unknown IGRA would have received preventative chemotherapy.

immunosuppression may be an overestimate. These data are, however, consistent with other studies documenting 84% and 78% of patients on immunosuppression at the time of IGRA [12, 13].

There are limitations to the study. TB reactivation could have occurred after data collection. Our median follow up of 2.4 years exceeded the median time for reactivation following TNF antagonists (3–18.5 months) [10, 15]. Only the London TB Register was searched. This could miss TB diagnoses outside London or in the case of name changes. However, given the patients' regular follow-up at the hospital, this seems unlikely. The study did not aim to determine the benefit of preventative chemotherapy in IGRA-positive patients, but evaluated the use of a negative IGRA for screening. The analysis and costings relate to a London hospital, with risk stratification performed within a TB clinic (as in other centres [13]), and would be different using alternative models. It was a retrospective study and, although further ethnicity data were collected prospectively, there were unavailable demographic and IGRA data. It is possible that some of these patients had IGRA results unavailable on EPRs or performed elsewhere, TST testing, or risk stratification. None of these patients went on to develop TB, so the message that a negative IGRA is sufficient for screening could only be strengthened by addition of this group (which may include further negative IGRAs). This aside, the conclusions and analysis remain valid when just accepting the 353 known IGRA-negative cases. A similar prospective study would require large numbers and long-term follow-up, especially as TB reactivation incidence is low.

A screening approach based on a negative IGRA in patients commencing TNF antagonists performed well in this population and reduced resource utilisation.

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A negative IGRA is an adequate pragmatic screening tool prior to starting TNF antagonists http://ow.ly/zYNgX

Georgia Woodfield[1], Benjamin Passey-Heaton[2], Anob Chakrabarti[1], Anton Pozniak[1,3] and Michael R. Loebinger[1,3,4]
[1]Chelsea and Westminster Hospital NHS Foundation Trust, London, UK. [2]St George's University of London, London, UK. [3]Imperial College, London, UK. [4]Royal Brompton and Harefield NHS Foundation Trust, London, UK.

Correspondence: Michael R. Loebinger, Royal Brompton Hospital, Sydney St, London SW3 6NP, UK.
E-mail: m.loebinger@rbht.nhs.uk

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