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Editorial

British Thoracic Society (BTS) recommendations for assessing risk and managing tuberculosis in patients due to start anti-TNF-α treatments

Anti-TNF drugs have revolutionized rheumatology practice. However, these new drugs have also created new problems that UK rheumatologists have rarely had to consider in their patients. In particular, a major concern is the propensity of patients on anti-TNF therapy to develop reactivation of latent tuberculosis (TB). A recent review in this journal has highlighted these problems [1]. The increase in TB associated with anti-TNF-α therapy is well documented for all three available anti-TNF drugs [2–4] and has resulted in manufacturers recommending tuberculin skin testing and other screening procedures for TB prior to commencing treatment. The British Society for Rheumatology (BSR) and the British Society for Gastroenterology have worked with the British Thoracic Society (BTS) in drawing up recommendations for: (i) assessing the risk of TB infection in patients due to start anti-TNF therapy, and (ii) the management of any TB infection present in patients either due to start or already treated with anti-TNF-α therapy.

These guidelines have been finalized and published in *Thorax* [5]. They need to be read carefully by all British rheumatologists and nurse specialists involved with anti-TNF therapy as they will impact on practice significantly. They highlight the importance of close liaison between clinicians prescribing anti-TNF therapies and TB specialists. The components of the guidelines that are relevant to a rheumatologist and that are likely to impact on clinical practice are summarized below.

Prior to commencing anti-TNF-α therapy, all patients should have their risk of TB assessed. This will include a history of any prior TB infection and treatment, a clinical examination and a chest X-ray. The chest X-ray needs to be taken as close as possible to the planned start date for anti-TNF-α therapy and with a minimum time interval of 3 months. The accuracy and reliability of tuberculin skin testing is significantly affected by immunosuppressive therapy [6]. Patients who are eligible for anti-TNF therapy according to NICE (National Institute for Clinical Excellence) guidelines [7] will be taking immunosuppressive medication in the majority of cases (especially methotrexate), thus rendering tuberculin testing unreliable. Tuberculin testing would only be indicated in patients planned for anti-TNF-α therapy who have not received recent immunosuppressive therapy. For patients who have previously received immunosuppressants but who are currently not being treated with them, the tuberculin test will only become reliable once treatment has been stopped for 1 month in the case of steroids and for 3 months in the case of all other immunosuppressants. Any patient with an abnormal chest X-ray or a past history of TB or TB treatment requires referral to a TB specialist. If the patient is found to have active TB, they require a full course of standard chemotherapy, and anti-TNF therapy should not be commenced. The BTS guidelines recommend that a full course of anti-TB therapy is completed prior to commencing anti-TNF-α treatment, but there may be circumstances in which, following liaison between the specialist in TB, a compromise can be made. Anti-TB treatment should be taken for at least 2 months (with full compliance) and/or until the drug susceptibility profile of the organism is known prior to commencing anti-TNF-α therapy.

If a patient with an abnormal chest X-ray or a past history of TB or TB treatment is deemed to have had previous adequate treatment by their TB specialist, they will require careful monitoring for any recurrence of their TB and a repeat chest X-ray after 3 months, but will be able to commence anti-TNF-α therapy without further investigation or treatment. If, however, previous treatment has been deemed to be inadequate by a TB specialist and if the risks of TB exceed the risks of chemoprophylaxis (using the algorithm supplied in the BTS guidelines), a full course of chemoprophylaxis should be completed prior to commencing anti-TNF-α therapy.

The majority of patients in UK practice will have a normal chest X-ray and no previous history of TB exposure. For such patients, the tuberculin test is indicated for the rare patient in whom immunosuppressant therapy has not been used prior to the planned start of anti TNF-α therapy. The BTS recommend that a TB specialist undertakes all tuberculin testing, but with appropriate training these tests may be undertaken by rheumatologists, with the agreement of local TB specialists.

For patients with a normal chest X-ray, no history of TB and no current or recent immunosuppressant therapy (1 month for steroids, 3 months for other immunosuppressants), a Heaf response of grade 0–2 or a Mantoux response of 0–14 mm, no further action is needed and anti-TNF-α therapy can be commenced provided the patient has had a previous BCG. For those who have not had a previous BCG, a Heaf grade of 0–1 or a Mantoux response of 0–5 mm also requires no further action and anti-TNF-α therapy can be commenced. All patients with higher-grade tuberculin responses require assessment of the risk of TB infection or reactivation *vs* the risk of TB chemoprophylaxis, using the algorithm supplied in the BTS guidelines. If the risk of side-effects of chemoprophylaxis is greater than the risk of acquiring TB, patients will be able to commence their anti-TNF-α therapy, but will need monitoring for any symptoms suggestive of TB and will require a chest X-ray after 3 months of treatment. If, however, the risk of TB outweighs the risks of chemoprophylaxis, patients will receive chemoprophylaxis, as recommended by a TB specialist, and treatment should be completed before the patient commences anti-TNF-α therapy.

The same assessment of the risk of TB infection or reactivation *vs* the risk of TB chemoprophylaxis would need to be undertaken for the vast majority of patients seen within a rheumatology department; i.e. those patients with a normal chest X-ray, no history of previous TB or TB treatment, and current or recent treatment with immunosuppressant therapy. In such patients, a tuberculin test is not helpful. In general, the patients in whom the risk of TB will outweigh the risk of chemoprophylaxis are black Africans over the age of 15, south Asians born outside the UK and patients from other ethnic groups who have been resident in the UK for less than 5 yr. For the majority of other patients, the risk of chemoprophylaxis will outweigh the risk of TB and no delay in starting anti-TNF-α therapy (through the need for TB chemoprophylaxis) will be required.

The BTS recommends that TB specialists undertake all risk assessments for chemoprophylaxis when indicated through use of the guidelines. However, with appropriate training, and following agreement with TB specialists at a local level, it may be possible for these to be undertaken by rheumatologists for patients with a normal chest X-ray and no history of TB, hence reducing the inevitable impact that these guidelines will have on TB specialists.

For patients requiring chemoprophylaxis, there are a number of regimes that can be used, but the BTS recommended regime is the longest (6 months) and needs to be completed prior to commencing anti-TNF-α treatment. In general, the shorter regimes are more toxic and therefore less desirable, but discussions are encouraged between rheumatologists and TB specialists at a local level with regard to the pros and cons of using shorter, but potentially more toxic, regimens in order to allow anti-TNF-α therapy to commence earlier on an individual case basis. Any patient who develops clinical features of TB during anti-TNF-α therapy requires referral to a TB specialist and a full course of anti-TB chemotherapy if TB is confirmed. Anti-TNF-α treatment may be continued in such patients if required. The BTS guidelines emphasize that symptoms and signs of TB need to be monitored in all patients receiving anti-TNF-α therapy, but also in patients who have discontinued treatment for a minimum of 6 months after stopping treatment.

In Derby we conducted an audit of 116 records of patients commenced on anti-TNF therapy [8]. It has been our local practice to perform a tuberculin test on all patients as part of the screening process for exposure to TB. On retrospectively applying the new guidelines, the number of tuberculin tests performed would have dropped to 31. Seven of our patients were receiving prophylactic isoniazid and two patients had been referred for advice from a TB specialist prior to commencing anti-TNF therapy. On applying the new guidelines, six patients would be advised to receive chemoprophylaxis, and a further eight would require assessment and an opinion from a respiratory specialist (four had a history of previous TB, two had an abnormal chest X-ray, and risk assessment suggested that two should be considered for chemoprophylaxis in consultation with a specialist). Our department has nurses with experience in administering and reading tuberculin tests, but without this, other departments may have to refer more patients to TB specialist services for tuberculin testing. Furthermore, different patient populations with more varied ethnic backgrounds within the UK are likely to require more opinions from TB specialists for risk assessment.

We conclude that the principle impact of the new guidelines would be a substantial decrease in tuberculin testing, but a small but significant increase in the requirement for TB specialist opinions. The requirement for TB specialist service involvement will vary with local expertise and with the ethnic diversity of the catchment populations. This needs to be discussed amongst local specialist service providers because of the potential pressure on resources.

In summary, the BTS guidelines for assessing risk and for managing TB infection in patients due to start anti-TNF-α treatment have now been published in *Thorax* and need to be read in detail by all UK rheumatologists and specialist nurses involved in the use of anti-TNF drugs. This document provides guidance on assessing the risk of developing TB in patients due to commence anti-TNF-α therapy. The guidelines are recommended by the BSR and should be used in all patients prior to commencing anti-TNF-α therapy. For the majority of rheumatology patients, tuberculin tests are not recommended and the risk of TB needs to be assessed through clinical history and examination, chest X-ray and, when required, use of the algorithm assessing the risk of TB *vs* the risk of chemoprophylaxis, as outlined in the guidelines. The resource implications of a greater use of TB specialist opinion will have to be considered in each hospital setting.

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