TB and anti-TNF-α treatment

Tuberculosis and anti-TNF-α treatment

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New evidence-based guidance on anti-TNF-α treatment is being developed by the Joint Tuberculosis Committee of the BTS in conjunction with the British Societies of Rheumatology and Gastroenterology

Anti-tumour necrosis factor (TNF) treatment for rheumatoid arthritis and Crohn's disease has been introduced over the last few years. Infliximab (Remicade; Schering-Plough), a humanised monoclonal antibody, is licensed for the treatment of both rheumatoid arthritis[1] and Crohn's disease,[2] while etanercept (Enbrel; Wyeth Laboratories), a fusion protein binding free TNF-α using the soluble portion of the TNFR-2 receptor,[3] and adalimumab (Humira; Abbott Laboratories), a fully humanised monoclonal antibody,[4] are licensed for treating rheumatoid arthritis. Post-marketing surveillance in the USA[5] has identified cases of tuberculosis (TB) associated with infliximab use and a smaller number with etanercept. TB cases have also been reported in association with adalimumab (Humira prescribing information, Abbott Laboratories, 2002). The cases associated with infliximab occurred within three cycles of treatment, with a median of 12 weeks from commencing treatment,[5] and most were in extrapulmonary sites.[6] Calculations have suggested that TB rates in patients in the USA treated with infliximab or etanercept are six times that of untreated patients.[7]

The increase in active TB in association with anti-TNF-α treatment has led to a requirement for patient screening for active and latent TB before anti-TNF treatment is given. However, the screening—which the manufacturers suggest should include tuberculin testing—introduces further complications. Firstly, in the study of infliximab, Keane *et al*[5] found that up to 79% of patients were receiving immunosuppressive therapy before anti-TNF treatment which would have precluded effective skin testing for TB. Secondly, in Europe, where the population may have received prior BCG vaccination, the interpretation of tuberculin tests is further complicated. Thirdly, chemoprophylaxis or preventive treatment for TB itself carries a risk—principally of drug induced hepatitis—which increases with age, varies with the chemoprophylaxis regimen, and can occasionally be fatal.

Clearly, persons found to have active TB or with evidence of previous TB disease which has not been adequately treated will need at least some anti-tuberculosis treatment before anti-TNF treatment can commence. However, since the majority of patients will not be assessable for prior TB infection by skin testing, a judgement of the individual risk of TB disease will have to be made. Within the UK, and probably in other developed countries, the individual risk of TB can vary markedly. In the UK the major determinants of risk are age, ethnicity and—for those born outside the UK—the length of time since first entry.[8] For example, the annual risk of disease can vary from 2/100 000 in a white person aged 15–34 years to 593/100 000 in a South Asian aged over 35 years who has been in the UK for less than 5 years. The ''individual risk'' would then need to be multiplied by five to allow for the additional effect of anti-TNF treatment and this derived figure would then have to be compared with the risk of significant hepatitis (level 3 or 4) from the proposed TB chemoprophylaxis regimen, with at least one regimen used in the USA (rifampicin and pyrazinamide for 2 months) being too toxic for use.[9] The risk of chemoprophylaxis compared with the chance of contracting TB will therefore favour observation in some individuals and TB chemoprophylaxis in others. In future, gamma-interferon production from whole blood and/or stimulated lymphocytes[10] may be able to determine whether patients receiving immunosuppressive treatment which interferes with tuberculin skin testing have been previously infected with TB, but an individual assessment of the risk/benefit ratio in such patients with respect to chemoprophylaxis will still be needed.

All these factors have led to many requests for guidance in this area. The Joint Tuberculosis Committee of the British Thoracic Society, a subcommittee of the Standards of Care Committee, is developing practical evidence-based guidance in conjunction with the British Societies of Rheumatology and Gastroenterology. In order to meet the AGREE criteria,[11] however, this will take some time. Initial draft proposals have been posted on the members' website for comment. There are, however, some concerns that this will be an additional workload for already stretched respiratory medicine specialists.

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