PREVENTING TB IN PATIENTS WITH CROHN’S DISEASE NEEDING INFLIXIMAB OR OTHER ANTI-TNF THERAPY

DS Rampton

Centre for Gastroenterology, Institute of Cell and Molecular Science, Barts and the London, Queen Mary School of Medicine & Dentistry, London E1 2AD, UK

Address: Prof DS Rampton, Endoscopy Unit, Royal London Hospital, London E1 1BB

Tel: +442073777442
Fax: +442073777441
Email: d.rampton@qmul.ac.uk

Key words: Crohn’s disease, ulcerative colitis, infliximab, tumour necrosis factor, tuberculosis.

Acknowledgements: I am grateful to Prof P Ormerod (British Thoracic Society Standards of Care Committee), and to members of the IBD Section (Chairman, Dr S Travis) and Clinical Services Committee (Chairman, Dr M Denyer) of the British Society of Gastroenterology for reviewing this paper and for their helpful suggestions.

Licence for Publication: The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted)
to be published in Gut editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence (http://gut.bmjjournals.com/misc/ifora/licenceform.shtml).

**Competing interest:** I have received financial support from Schering-Plough (UK) for CME purposes including flights and accommodation for Digestive Diseases Week in Chicago, May 2005.
SUMMARY

The increased risk of active tuberculosis (TB) associated with infliximab makes necessary a screen for active and latent TB before this or other antiTNF treatment is begun in patients with Crohn’s disease. This paper outlines how such screening should be undertaken, and how to decide which patients need antituberculous treatment or chemoprophylaxis before infliximab. All patients need a careful history for TB and a chest Xray. The minority of patients with a history of TB or an abnormal chest Xray should be referred for assessment by a TB specialist. Of the remainder, those with Crohn’s disease who are on immunosuppressive therapy do not require tuberculin testing. Comparison of their risk of TB while on antiTNF therapy with the risks of chemoprophylaxis-induced hepatitis indicates that black Africans aged over 15 years, S Asians born outside the UK and other ethnic groups resident in the UK for less than 5 years should be considered for chemoprophylaxis with isoniazid for 6 months. For how to minimise the risk of TB in the small minority of patients with IBD not on immunosuppressive treatment, readers are referred to the more detailed guidelines published in Thorax.

INTRODUCTION

Infliximab is of proven benefit in the treatment of chronic active Crohn’s disease (1) as well as in rheumatoid arthritis (2) and ankylosing spondylitis (3); preliminary data suggests it may also have a therapeutic role in refractory active ulcerative colitis (4-6). An increased risk of TB was noted soon after the introduction of infliximab in the late 1990s. To address the question of how best to prevent TB in patients needing infliximab and other antiTNF therapies, the British Thoracic Society Standards of Care Committee formed a sub-committee chaired by Prof Peter Ormerod and comprising also
representatives of the British Society of Rheumatology and British Society of Gastroenterology (DSR). The full recommendations of this group, and their rationale, are reported in Thorax (7; on-line at http://thorax.bmjournals.com/cgi/rapidpdf/thx.2005.046797v1). This brief article aims to bring to the attention of gastroenterologists the principal conclusions as they relate specifically to management of patients with Crohn’s disease; to facilitate this aim, an algorithm which outlines the approach to minimising the risk of TB is provided (Figure).

**WHAT IS THE RISK OF TB?**

In the general population in the UK, the incidence of TB depends on a range of factors which include age, ethnicity and country of birth (8). The annual risk of TB in the UK is increased at least 30-fold in black Africans aged over 15 years, and in South Asians born outside the UK; it is even greater in people from other ethnic groups resident in the UK for less than 5 years (7).

In Crohn’s disease which has not been treated with infliximab the incidence of TB is unknown; indeed, in some patients it may of course be difficult, initially at least, to distinguish the one diagnosis from the other. Infliximab appears to increase the background risk of TB about 5-fold in both Crohn’s disease and rheumatoid arthritis (7), most, although not all, cases being extra-pulmonary and occurring within the first 3 months of treatment (9-13). Although the incidence of infliximab-related TB may now be falling due to improved risk assessment, chemoprophylaxis (see below) and/or reporting fatigue (11), complacency is clearly inappropriate: the mortality of TB in the early days of its recognition in association with use of infliximab approached 10%.
HOW CAN THE RISK OF TB BE MINIMISED IN PATIENTS TO BE GIVEN INFLIXIMAB? (Figure)

Recommendations from several sources, including the European Agency for Evaluation of Medicinal Products (EMEA) and the National Institute for Clinical Excellence (NICE) (see below), agree that patients in whom use of anti-TNF therapy is being considered should be meticulously questioned about prior TB and its treatment, and have a chest X-ray taken (7, 12-16).

**Patients with a history of TB and/or abnormal chest Xray.** Patients with a history of TB or an abnormal chest Xray should be referred directly to a specialist with expertise in TB (7). Those with active TB should receive standard antituberculous chemotherapy for at least 2 months before starting on infliximab. Patients with a chest Xray showing previous TB, or with a history of previous extra-pulmonary TB which has been fully treated, should be carefully monitored during infliximab therapy; those in whom treatment may have been inadequate should have active TB excluded by appropriate investigation and should be given chemoprophylaxis for 2 months before starting infliximab.

**Patients with no history of TB and normal chest Xray.** Some guidelines have suggested that a tuberculin test should be used to direct the optimal approach in this group of patients (1,12,13). Recent data, however, has confirmed a very high incidence of anergy in patients with Crohn’s (14), and the EMEA recommendations specifically warn prescribers of the risk of false negative skin test results in severely ill or immunocompromised patients with Crohn’s disease (15; on-line at http://www.emea.eu.int/pdfs/human/press/pus/003202.pdf). Indeed, since under existing (2002) NICE guidelines (16; on-line at http://www.nice.org.uk/pdf/NiceCROHNS40GUIDANCE.pdf) all patients with Crohn’s
disease in the UK needing infliximab will be chronically ill and currently or recently
taking corticosteroids and/or immunomodulatory drugs, tuberculin testing will not assist
in decision-making and is considered unnecessary (7). (There is no data about the
incidence of anergy to tuberculin in patients with ulcerative colitis; in these, currently
exceptional patients, the guidelines described in full in reference (7) should be followed).

What does need to be considered is the annual risk of TB in individual patients to
be given infliximab: as indicated above, this is increased about 5-fold by infliximab, and
still further in some ethnic groups. This risk needs to be balanced against the risk of side-
effects caused by TB chemoprophylaxis, which is dependent on the regime to be used (7).
The commonest regime, isoniazid for 6 months, has a hepatitis risk rate of about
280/100000 treated patients (7). Two shorter regimes, rifampicin with isoniazid for 3
months, and rifampicin with pyrazinamide for 2 months, cause serious hepatitis much
more often (1800 and 6600/100000 treated patients, respectively) (7).

These considerations mean that, in general, Caucasians in the UK with no history
of TB, and a normal chest Xray, need no TB chemoprophylaxis. In contrast, even if they
have no TB history, and their chest Xray is normal, black Africans aged over 15, South
Asians born outside the UK, and other ethnic groups resident in the UK for less than 5
years have such a high risk of TB while on infliximab that they should usually be offered
isoniazid for 6 months when starting it (7). In other non-Caucasian ethnic groups, data on
the risk of TB is too limited for it to be possible to make definitive recommendations.

**Monitoring for TB in patients on infliximab.** All patients on infliximab
should be monitored carefully for symptoms such as fever, weight loss or cough:
gastroenterologists should be alert to the possibility of extra-pulmonary as well as the
more familiar lung disease. The slightest suspicion of TB should prompt immediate
referral to a specialist TB physician.
CONCLUSIONS.

Tuberculosis is one of the most serious complications of the use of infliximab. In each patient in whom therapy with infliximab is being considered, a plan should be drawn up based on their history, chest Xray, ethnicity, place of birth and duration of residence in the UK (Figure). Implementation of these recommendations is likely to reduce dramatically the risk of TB in patients given infliximab and other antiTNF agents.
Figure. Algorithm to indicate the approach to prevention of tuberculosis (TB) in patients on immunosuppressants who need infliximab or other anti-TNF-alpha therapy for Crohn’s disease. The high incidence of anergy in patients with Crohn’s disease who take immunosuppressants (14, 15) makes tuberculin skin testing unreliable and unnecessary. The decision about TB chemoprophylaxis in individual patients with no history of TB and a normal chest Xray is dependent on a comparison of their ethnicity-related risk of...
acquiring TB during anti-TNF therapy, and the risk of drug-induced hepatitis during chemoprophylaxis (see text and ref 7). (For recommendations about the prevention of TB in the small minority of patients with Crohn’s disease not taking concomitant immunosuppressive therapy, and in those with ulcerative colitis in whom infliximab is being considered, see ref 7). CXR denotes chest Xray.
REFERENCES
Preventing TB in patients with Crohn's disease needing Infliximab or other anti-TNF therapy

David S Rampton

Gut  published online August 19, 2005

Updated information and services can be found at:
http://gut.bmj.com/content/early/2005/08/19/gut.2005.076034.citation

These include:

Supplementary Material
Supplementary material can be found at:
http://gut.bmj.com/content/suppl/2005/09/09/gut.2005.076034.DC1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/