Annals of the American Thoracic Society

Minimizing tuberculosis risk in patients receiving anti-TNF therapy

Journal:	*Annals of the American Thoracic Society*
Manuscript ID	Draft
Manuscript Type:	ED - Editorial
Date Submitted by the Author:	n/a
Complete List of Authors:	Esmail, Hanif; University of Cape Town, Wellcome Center for Infectious Diseases Research in Africa; University of Oxford Medical Sciences Division, Radcliffe Department of Medicine Wilkinson, Robert; The Francis Crick Institute; University of Cape Town, Wellcome Center for Infectious Diseases Research in Africa; Imperial College London, Medicine
Subject Category:	MYCOBACTERIAL DISEASES, 11.01 Diagnosis of Tuberculosis or Latent Infection < MYCOBACTERIAL DISEASES, 11.04 Mycobacterial Disease: Host Defenses < MYCOBACTERIAL DISEASES, 10.06 Host Defenses to Microbial Pathogens < MICROBIOLOGY AND PULMONARY INFECTIONS
Key Words:	Anti-TNF agents, latent tuberculosis, drug prevention

Title: Minimizing tuberculosis risk in patients receiving anti-TNF therapy

Authors: Hanif Esmail[1,2] and Robert J. Wilkinson[1,3,4]

1. Wellcome Center for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine and Department of Medicine, University of Cape Town, Observatory 7925, Republic of South Africa
2. Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom
3. Department of Medicine, Imperial College London, W2 1PG, United Kingdom
4. The Francis Crick Institute, London, NW1 2AT United Kingdom

Words: 1241

References: 17

Article:

Systemic anti-tumor necrosis factor (TNF) therapy has improved the management of immune-mediated inflammatory conditions, such as rheumatoid arthritis, psoriasis and inflammatory bowel disease (IBD), by neutralizing TNFα which contributes to inflammation at the site of disease. TNFα, however, is also an important cytokine for macrophage activation and of critical importance in host control of *Mycobacterium tuberculosis* (Mtb)(1). As a result anti-TNF therapies (in particular monoclonal antibody preparations such as infliximab and adalimumab) are associated with a moderate risk of reactivating latent tuberculosis (TB) of approximately 2-8 fold(2, 3). Of those that develop disease, the majority do so within 3-6 months of commencing infliximab and mortality can be considerable(4). Screening for TB prior to commencing anti-TNF therapy is therefore important and many guidelines have been developed recommending a variety of approaches to TB screening(5). Evaluation of these approaches is often difficult as the TB incidence in many countries where anti-TNF therapy is most commonly prescribed, is low. For example in a recent study in the USA covering 7210 person years follow-up of patients with IBD prescribed anti-TNF therapy, 72-86% of patients received TB screening and only 2 patients developed TB(6).

In this issue Lee and colleagues report a cohort of 10,863 patients commenced on anti-TNF therapies for a variety of indications between 2011 and 2013 in South Korea, a country with an intermediate TB burden (TB incidence 86/100,000). The study was conducted following the introduction of national guidelines for TB screening prior to anti-TNF therapy. These guidelines recommended patients be screened for latent infection by either an interferon gamma release assay (IGRA) or

tuberculin skin test (TST) with 10mm cut-off, along with chest radiograph (CXR) prior to anti-TNF therapy(7). The incidence of TB was ascertained through analysis of national insurance claims according to whether or not they had received prior preventive drug therapy with rifampin, isoniazid or both (PT). The incidence of active TB was significantly lower in the 22.7% who received any PT compared to those that hadn't (4.07/1000 person years vs 12.34/1000 person years (incidence rate ratio (IRR) 0.33)) with the risk reduction being greatest in those that completed a full course of PT, highlighting the importance of adherence. The strength of the study was its population coverage, utilising a database covering nearly 100% of residents in South Korea. The study is therefore a valuable programmatic evaluation of TB screening at national level in those commencing anti-TNF therapy, highlights the value of PT, and shows that a substantial number of cases of TB (over 100 in 3 years) occurred in patients that did not receive prior PT. A limitation of the study was that the authors did not have access to TB screening data and were therefore not able to shed light on whether these findings reflected to a failure to implement guidelines or whether the guidelines, though implemented correctly, failed to identify all those at risk of reactivation. Evidence from a smaller study in Korea showed that by 2013, screening by IGRA occurred in up to 90% of patients, although TST was performed in less than 40%(8). Other possible explanations for the high rates of TB in those not receiving PT are that patients declined PT or that infection was acquired following screening. The findings by Lee *et al* likely reflect all these factors.

In the absence of a true gold standard for latent TB there is fundamental question about the best approach to identify people asymptomatically infected with viable Mtb, with potential to reactivate, which is particularly important in the context of anti-TNF therapy. Current tests for latent TB (TST and IGRA (QuantiferonTB-Gold and T-SPOT-TB)) are immunodiagnostics that merely demonstrate immune sensitization by detecting a cell-mediated immune response following *in vivo* or *ex vivo* stimulation with mycobacterial antigens. They do not indicate the presence of viable Mtb and often remain positive following treatment(9). In addition, conditions or therapies which impair cell mediated immune responses may compromise sensitivity of these tests. Approximately 80% of patients for whom anti-TNF therapy is being considered are on immunosuppressive, disease modifying agents (DMARDS) that frequently include corticosteroids(8, 10). Steroid prescription at the time of TST is associated with increased likelihood of a negative result, and for this reason IGRA are becoming the preferred investigation for latent TB in patients receiving DMARDS(11). However, the IGRA result may also be affected by steroid use in particular by increasing the likelihood of an indeterminate result(12). Relying on a single IGRA result to guide PT, which may have been the case in many patients in study by Lee *et al*, may be inadequate in high-risk populations. Discordance

between positive TST (sometimes strongly positive) and negative IGRA is common as is discordance between QuantiferonTB-Gold and T-SPOT.TB(13). Boosting of the TST response by repeat two-step testing, as is recommended in some guidelines including Korean, may increase likelihood of a positive result but increases logistical complexity and is often not performed(14). The likelihood of a positive IGRA may also be boosted by a prior TST, as we have recently shown in HIV-1 co-infected patients, although this has yet to be investigated in patients taking DMARDS(15). Given the limitations of these immunodiagnostics in this high-risk population some guidelines additionally favour providing PT based on epidemiological risk. For example, in the United Kingdom, PT is recommended for those in whom the annual risk of TB (on anti-TNF therapy) would exceed the risk of hepatotoxicity with PT, e.g. those born in South Asia or Africa(3). Extending criteria for PT is not without consequences. It inevitably increases the number needed to treat to prevent a case of TB, leading to unnecessary adverse events and delays in initiating anti-TNF therapy all of which needs to be taken into consideration along with cost-effectiveness.

The timing of TB screening is often prior to commencing anti-TNF but the duration of such therapy may be prolonged. Patients re-infected while on anti-TNF therapy may be at high risk of progression to disease. This may be particularly relevant in countries like Korea with higher burdens of TB. In a recent French/Swiss study of 44 cases of TB occurring in patients following anti-TNF therapy who had an initially negative TB screen (25 by TST alone, 15 IGRA+/- TST), 57% of cases occurred more than 12 months after initiation of therapy and 36% had risk factors for exposure to TB following anti-TNF therapy. This suggests that the initial screen may be truly negative in some cases with subsequent infection and that consideration of ongoing screening in patients at risk of TB exposure may be indicated(16). In the study by Lee *et al* the time between prescription of anti-TNF therapy and TB therapy was not discussed which may have been informative of whether cases were related to reactivation or re-infection.

Current tests for latent TB are suboptimal. A next generation of tests are proposed for which target product profiles are under development; a test for incipient TB with high predictive value for developing TB and a test for persistent infection which if negative would rule out risk of reactivation are desirable(17). Pending the potential development of such tests, screening algorithms need to be optimised to the circumstances of individual countries, there is no one size fits all solution. Non-adherence with guidelines has been shown to increase probability of developing TB(14). Monitoring of adherence to, and efficacy of, TB screening is critical and additional studies such as that by Lee *et al* will be valuable in providing an overview of the effectiveness of such programs.

References:

1. Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. Clin Exp Immunol. 2010;161(1):1-9.

2. Horsburgh CR, Jr., Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. N Engl J Med. 2011;364(15):1441-8.

3. Ledingham J, Wilkinson C, Deighton C. British Thoracic Society (BTS) recommendations for assessing risk and managing tuberculosis in patients due to start anti-TNF-{alpha} treatments. Rheumatology (Oxford). 2005;44(10):1205-6.

4. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345(15):1098-104.

5. Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2010;36(5):1185-206.

6. Hou JK, Kramer JR, Richardson P, Sansgiry S, El-Serag HB. Tuberculosis Screening and Reactivation Among a National Cohort of Patients with Inflammatory Bowel Disease Treated with Tumor Necrosis Factor Alpha Antagonists. Inflamm Bowel Dis. 2016.

7. Lee SH. Diagnosis and treatment of latent tuberculosis infection. Tuberc Respir Dis (Seoul). 2015;78(2):56-63.

8. Kim ES, Song GA, Cho KB, Park KS, Kim KO, Jang BI, et al. Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. World J Gastroenterol. 2015;21(11):3308-16.

9. Esmail H, Barry CE, 3rd, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. Philos Trans R Soc Lond B Biol Sci. 2014;369(1645):20130437.

10. Singanayagam A, Manalan K, Sridhar S, Molyneaux PL, Connell DW, George PM, et al. Evaluation of screening methods for identification of patients with chronic rheumatological disease

requiring tuberculosis chemoprophylaxis prior to commencement of TNF-alpha antagonist therapy. Thorax. 2013;68(10):955-61.

11. Belard E, Semb S, Ruhwald M, Werlinrud AM, Soborg B, Jensen FK, et al. Prednisolone treatment affects the performance of the QuantiFERON gold in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection. Inflamm Bowel Dis. 2011;17(11):2340-9.

12. Wirth T, Hildebrand F, Allix-Beguec C, Wolbeling F, Kubica T, Kremer K, et al. Origin, spread and demography of the Mycobacterium tuberculosis complex. PLoS Pathog. 2008;4(9):e1000160.

13. Vassilopoulos D, Tsikrika S, Hatzara C, Podia V, Kandili A, Stamoulis N, et al. Comparison of two gamma interferon release assays and tuberculin skin testing for tuberculosis screening in a cohort of patients with rheumatic diseases starting anti-tumor necrosis factor therapy. Clin Vaccine Immunol. 2011;18(12):2102-8.

14. Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum. 2007;57(5):756-61.

15. Esmail H, Thienemann F, Oni T, Goliath R, Wilkinson KA, Wilkinson RJ. QuantiFERON conversion following tuberculin administration is common in HIV infection and relates to baseline response. BMC Infect Dis. 2016;16(1):545.

16. Abitbol ~~Y~~, Laharie D, Cosnes J, Allez M, Nancey S, Amiot A, et al. Negative Screening Does Not Rule Out the Risk of Tuberculosis in Patients with Inflammatory Bowel Disease Undergoing Anti-TNF Treatment: A Descriptive Study on the GETAID Cohort. J Crohns Colitis. 2016;10(10):1179-85.

17. Cobelens F, Kik S, Esmail H, Cirillo DM, Lienhardt C, Matteelli A. From latent to patent: rethinking prediction of tuberculosis. The Lancet Respiratory Medicine. 2016.

Acknowledgements

RJW is supported by the Francis Crick Institute which receives its core funding from Cancer Research UK (FC00110218), the UK Medical Research Council (FC00110218), and the Wellcome Trust (FC00110218). He also receives funding from the Wellcome Trust (104803, 203135), National Institutes of Health (U19 AI 111276) and National Research Foundation of South Africa (96841).

Formatted: Font: 11 pt