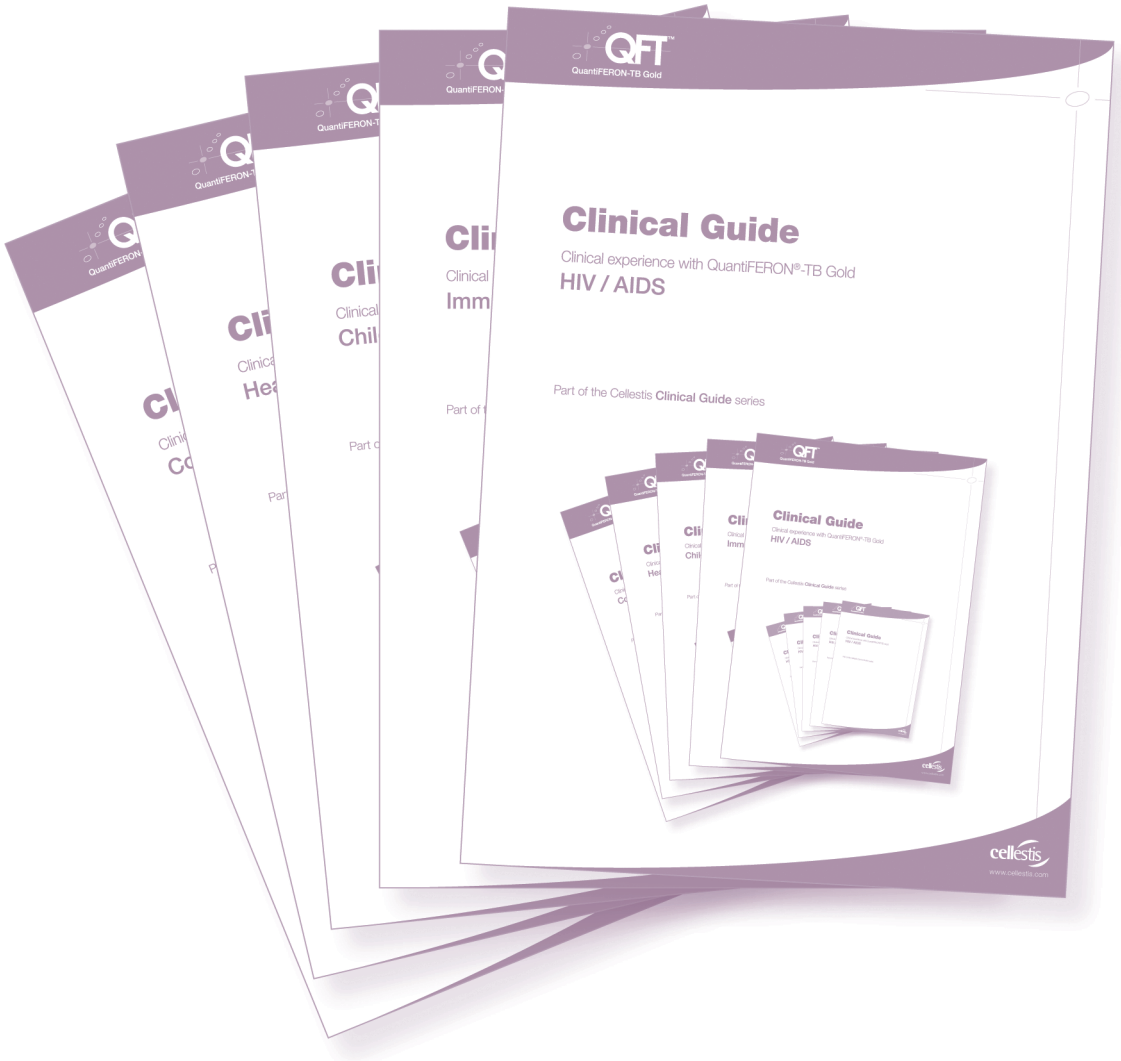
QFT®
QuantiFERON-TB Gold

Clinical Guide

Clinical experience with QuantiFERON®-TB Gold

TNF Blocker (Immunosuppressive) Therapy



cellestis

This clinical guide is intended to provide healthcare professionals with an overview of key clinical information and benefits of using QuantiFERON-TB Gold (QFT®) for tuberculosis (TB) testing in individuals being considered for tumor necrosis factor-alpha (TNF) blocker therapy or other immunosuppressive treatments.

Common Questions

Why does one need to screen for latent TB in individuals needing immunosuppressive therapy?

In patients receiving immune suppressive therapy, most cases of TB may be attributed to reactivation of tuberculosis infection, also known as Latent TB Infection (LTBI).[1,2,3] For patients on TNF-blocker therapy (including Enbrel®, Humira®, Remicade®) there is a greatly increased risk for those with LTBI to progress to active TB disease.[1] For example, in the US infliximab has been shown to increase the risk of TB in patients with rheumatoid arthritis (RA) from 6.2 cases to 52.5 cases per 100,000 patient-years of exposure,[2] with even higher rates reported in other countries (Table 1). A similar pattern of TB risk is seen in patients taking steroid hormone therapy, with studies showing patients taking such therapy (including dexamethasone, prednisolone) have a greater than 5 times increased risk of LTBI reactivation to active TB compared to the general population.[1,4] As a result, testing patients for active and latent TB infection is an extremely important precautionary measure before initiating[5] and during TNF-blocker and other immunosuppressive therapies.

Table 1 Ponce de Leon, *IJTLD June 2010*[28]

Incidence (x100,000) / Country	TB in general population	TB in rheumatoid arthritis	TB in rheumatoid arthritis with anti-TNF therapy
USA[2]	5.8	6.2	52.5
Spain[6]	21	95	1,113
Korea[7]	67.2	257	2,558
Peru[8]	122	216	—

TB can be difficult to treat in patients who receive TNF-blocker therapy or other immunosuppressive agents and the response to treatment can be unpredictable.[9] Additionally, the occurrence of immune reconstitution syndrome is of paramount concern in patients who have been treated with TNF-alpha blockers and developed active TB.[10,11] For these reasons screening for LTBI is advised for all patients before the use of TNF-alpha blockers. As an example, in October 2001, the US Food and Drug Administration (FDA) modified infliximab labelling to include a warning about infliximab-associated TB. The warning included instructions to screen for TB, treat LTBI prior to initiating anti-TNF therapy, and to monitor for TB during infliximab therapy.[12]

What are the limitations of the TST in individuals receiving immunosuppressive therapy?

The TST is widely used in the assessment of individuals with suspected TB infection—despite its well-known limitations. A variety of factors—other than infection with *M. tuberculosis*—are known to induce a positive TST result. These include Bacille Calmette-Guérin (BCG) vaccination, exposure to non-tuberculous mycobacteria, the inherent inability of the test to distinguish current infection from past resolved infection and subjectivity when reading and interpreting the test results. Additionally, studies have shown a high prevalence of TST anergy in the presence of immunosuppressive therapy.[13,14]

After the FDA warning about infliximab-associated TB, there were 130 reports received by the FDA (between 1st November 2001 and 30th May 2006) of TB in patients treated with infliximab. Of these 130 patients, 19 died. In an analysis of TST results in a subset of 67 cases, 47 patients (70%) had received a TST prior to initiation of therapy. Clearly demonstrating the suboptimal performance of the TST in these immunosuppressed patients, 34 (or approximately 75%) had a negative TST result.[15]

As the TST has limited sensitivity in patients who are already on immunosuppressive therapy, a more accurate method of detecting TB infection is required.

What other testing options are available?

Improved testing for TB infection is now available. QFT, a simple blood test, is a novel approach in the diagnosis of TB infection. Belonging to a new class of tests called interferon-gamma release assays (IGRAs), QFT is a modern alternative to the subjective, 110-year-old tuberculin skin test (TST or Mantoux test). Previously, the CDC guidelines stated that an IGRA can be used in all situations in which the skin test has been used. The 2010 updated CDC tuberculosis testing guidelines[16] recommend IGRAs as the preferred TB testing method in populations that are BCG vaccinated and those that are unlikely to return for a TST reading.

Screening for TB infection using QFT has several advantages. With results generally available within 24 hours, QFT is much quicker than the skin test and the patients do not have to come back 2 to 3 days later to have their test read. QFT is not confounded by Bacille Calmette-Guérin (BCG) vaccination, exposure to most non-tuberculous mycobacteria, or subjective interpretation, all factors which lead to the high number of false-positive results seen with the TST.

The high specificity of QFT (>99%) virtually eliminates the risk of false-positives, a common occurrence in skin tests. This alone reduces unnecessary TB prophylaxis and the potentially detrimental side effects of such therapy. Furthermore, QFT is consistently shown in published studies to be more sensitive than TST in immunosuppressed patients, not only those with inflammatory disease, but also for patients with chronic renal failure, diabetes mellitus, malignancies, and other immunosuppressive conditions.[17] These results indicate QFT has considerable benefits over the TST and provides healthcare professionals with a greatly improved diagnostic tool with better positive predictive value for TB infection than the traditional TST.[18]

What guidelines exist and what do they recommend?

Screening for TB infection and disease prior to TNF blocker therapy and during its use is a highlighted warning in the Remicade® (infliximab), Enbrel® (etanercept), and Humira® (adalimumab) product labeling. Recently, several national TB testing guidelines have been updated to reflect the benefits of using QFT to assess patients for TB infection prior to initiating TNF blocker therapy. The 2009 recommendations issued by the German Central Committee for the Fight Against Tuberculosis (DZK) call for exclusion of active TB and screening for latent TB infection using an IGRA before commencing a patient with autoimmune disease on TNF-blocker therapy.[18] Similarly, Swiss pneumology, rheumatology and gastroenterology experts compiled recommendations in 2007 mandating that prior to undergoing TNF blocker therapy, all patients should be screened for active TB disease and latent TB infection using an IGRA combined with detailed history and chest X-ray.[19] The authors added that the "use of TST is no longer recommended for screening in view of [its] limitations. Even a history of positive TST should be confirmed by an IGRA test."

TNF-blocker guidelines and recommendations

Germany	Diel *et al*. Pneumologie 2009 Jun;63:329-34. http://www.springerlink.com/content/c746084833106414/
United Kingdom	http://guidance.nice.org.uk/CG33
France	http://www.has-sante.fr/portail/display.jsp?id=c_490559
Switzerland	Beglinger *et al*. Swiss Med Wkly 2007; 137:620-2.

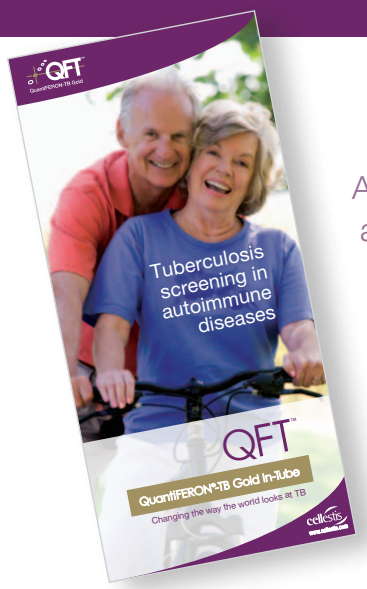
Summary of key highlighted studies

Publication	Main Finding
Winthrop KL, *Adv Rheum 2010.* [29]	The introduction of immunosuppressive therapies to treat rheumatoid arthritis (RA) has lead to an increased risk of tuberculosis for those patients. Specifically, anti-tumor necrosis factor therapy requires prior testing for tuberculosis. IGRAs, such as QuantiFERON-TB Gold (QFT) are now replacing the skin test in many clinical protocols as the diagnostic tool for TB infection. This article reviews screening strategies, and preventive and therapeutic options for TB control in RA patients.
Solovic *et al. Eur Resp J 2010.* [20]	Following TNF antagonist therapy, the relative risk for tuberculosis is increased up to 25 times, depending on the clinical setting and the TNF antagonist used. Interferon-gamma release assays (or, as an alternative in individuals without a history of Bacille Calmette Guérin vaccination, tuberculin skin testing) is recommended to screen all adult candidates for TNF antagonist for the presence of latent infection with *M. tuberculosis*. Moreover, pediatric practice suggests concomitant use of both the tuberculin skin test and an interferon-gamma release assay, as there are insufficient data in children to recommend one test over the other. Consequent targeted preventive chemotherapy is highly recommended for all individuals with persistent *M. tuberculosis* specific immune responses undergoing TNF antagonist therapy as it significantly reduces the risk of progression to tuberculosis. This TBNET consensus statement summarizes current knowledge and expert opinions and provides evidence-based recommendations to reduce the tuberculosis risk among candidates for TNF antagonist therapy.
Ponce de Leon *et al. J Rheumatol 2008.* [21]	Results demonstrated that QFT is more sensitive than the TST in RA patients. They also confirmed previous findings that the TST is severely compromised in RA patients. QFT was unaffected by current use of immunosuppressive drugs (including corticosteroids and methotrexate). Additionally, the rate of indeterminate QFT results in RA patients taking immunosuppressive medications was low at 1.9% (2/106).
Bocchino *et al. Eur J Clin Microbiol Infect Dis 2008.* [22]	QFT results correlated better with risk factors for LTBI than did those for the TST in inflammatory disease patients due to start TNF-blocker therapy; QFT was positive in 14 of 15 patients with risk factors, whereas TST was only positive in 8 of those 15 cases.
Cobanoglu *et al. Int J Tuberc Lung Dis 2007.* [23]	In the study of BCG-vaccinated inflammatory disease patients, 10 out of 97 patients (10.3%) prior to commencement of TNF-blocker therapy had a positive QFT result while 49 patients (50.5%) were TST-positive. The results demonstrated that QFT was more reliable than TST in detecting TB infection in these patients before initiation of TNF-blocker therapy.

QuantiFERON-TB Gold

References

1. Winthrop KL, *et al.* Tuberculosis associated with therapy against tumor necrosis factor alpha. *Arthritis Rheum 2005; 52:2968–74.*
2. Wolfe F, *et al*. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum 2004; 50:372–9.*
3. Wallis RS, *et al.* Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis 2004; 38:1261–5.*
4. Cisneros JR, *et al*. Corticosteroids in tuberculosis. *Ann Pharmacother 1996; 30:1298–303.*
5. Laffitte E, *et al*. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-gamma release assay vs. tuberculin skin test. *British J Dermatol 2009; 161:797–800.*
6. Gómez-Reino JJ, *et al*. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum 2003; 48:2122–7.*
7. Seong SS, *et al*. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. *J Rheumatol 2007; 34:706–11.*
8. Gamboa R, *et al.* Tuberculosis risk in patients with rheumatoid arthritis in an underdeveloped country with high tuberculosis prevalence [abstract]. *Arthritis Rheum 2004; 50:Suppl:S129.*
9. Garcia Vida C, *et al*. Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. *Clin Infect Dis 2005; 40:756–9.*
10. Arend SM, *et al.* A patient with de novo tuberculosis after discontinuing infliximab. *Int J Tuberc Lung Dis 2007; 45:1470–5.*
11. Belknap R, *et al.* Immune reconstitution to *Mycobacterium tuberculosis* after discontinuing infliximab. *Int J Tuberc Lung Dis 2005; 9:1057–8.*
12. Remicade (product label). *Accessed at http://www.fda.gov/medwatch/safety/2006/Oct_pls/Remicade_PI.pdf On 10th December 2007.*
13. Mow WS, *et al.* High incidence of anery in inflammatory bowel disease patients limits the usefulness of PPD screening before infliximab therpy. *Clin Gastroenterol Hepatol 2004; 2:309–13.*
14. Ponce de León D, *et al.* Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis. *Ann Rheum Dis 2005; 64:1360–1.*
15. Raval A, *et al.* Brief Communication: characteristics of spontaneous cases of tuberculosis associated with infliximab. *Ann Intern Med 2007; 147:699–702.*
16. Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection—United States, 2010. *MMWR June 25, 2010, Vol 59, No. RR-5.*
17. Kobashi Y, *et al*. Clinical evaluation of QuantiFERON TB-2G test for immunocompromised patients. *Eur Resp J 2007; 30:945–50.*
18. Diel R, *et al.* Recommendations for tuberculosis screening before initiation of TNF-alpha-inhibitor treatment in rheumatic diseases. *Pneumologie 2009 63:329–34. German.*



A patient brochure is available from Cellestis and may be distributed to your patients. Please email **info@cellestis.com** to request brochures for your clinic or practice.

19. Beglinger C, *et al*. Screening for tuberculosis infection before the initiation of an anti-TNF-alpha therapy. *Swiss Med Wkly 2007; 137:620–2.*
20. Solovic I, *et al*. The risk of tuberculosis related to TNF antagonist therapies: a TBNET consensus statement. *Eur Resp J 2010 Jun 7. [Epub ahead of print]*
21. Ponce de Leon D, *et al*. Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. *J Rheumatol 2008: 35:776–81.*
22. Bocchino *M, et al*. Performance of two commercial blood IFN-gamma release assays for the detection of *Mycobacterium tuberculosis* infection in patient candidates for anti-TNF-alpha treatment. *Eur J Clin Microbiol Infect Dis 2008; 27:907–13.*
23. Cobanoglu N, *et al*. Interferon-gamma assays for the diagnosis of tuberculosis infection before using tumour necrosis factor-alpha blockers. *Int J Tuberc Lung Dis 2007; 11:1177–82.*
24. Mori T, *et al.* Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens. *Am J Respir Crit Care Med 2004: 170:59–64.*
25. Pai *M, et al*. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med 2008; 149(3):177–84.*
26. Diel R, *et al.* Comparative performance of tuberculin skin test, QuantiFERON-TB-Gold In Tube assay, and T-Spot.TB test in contact investigations for tuberculosis. *Chest 2009; 135:1010–8.*
27. Diel R, *et al.* Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. *Am J Respir Crit Care Med 2008; 177:1164–70.*
28. Ponce de Leon D. Comparison of IGRAs with TST for the detection of LTBI in RA patients in a TB endemic population. *IJTLD 2010; vol. 14(6):S40-1.*
29. Winthrop KL, The risk and prevention of tuberculosis: Screening strategies to detect latent tuberculosis among rheumatoid arthritis patients who use biologic therapy. Advances in Rheumatology 2010; 8(2):43–52.

For more information, please contact the Cellestis office nearest you or visit **www.cellestis.com**

World Headquarters
Cellestis Limited
Email: info@cellestis.com
Tel: +61 3 8527 3500

Europe / Middle East / Africa
Cellestis GmbH
Email: europe@cellestis.com
Tel: +49 6151 428 59 0

Australia / New Zealand
Cellestis International
Email: quantiferon@cellestis.com
Tel: +61 3 8527 3500

North America / South America
Cellestis Inc.
Email: customer.service@cellestis.com
Tel: +1 661 775 7480 (outside USA)
Toll free: 800 519 4627 (USA only)

Japan / Korea
Cellestis Asia KK
Email: quantiferon@cellestis.com

Asia / Pacific
Cellestis AP Pte Ltd
Email: asiapac@cellestis.com
Tel: +65 6322 0822

cellestis

M05995182B