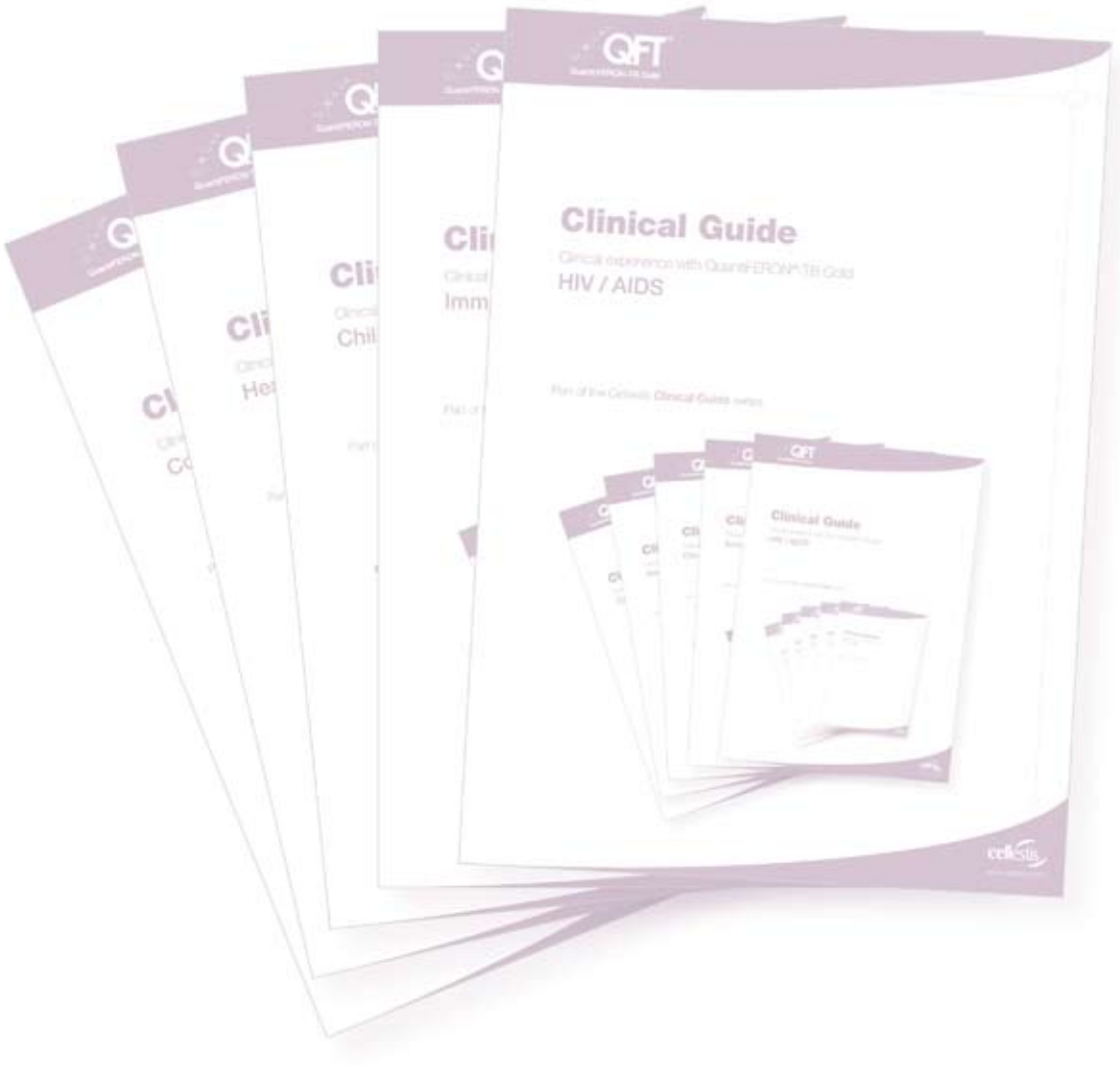
QFT™
QuantiFERON-TB Gold

Clinical Guide

Clinical experience with QuantiFERON®-TB Gold

Immunosuppressive Therapy



Cellestis Clinical Guide series 2008

cellestis
www.cellestis.com

This clinical guide is intended to provide healthcare professionals with an overview of current clinical information on the use of QuantiFERON®-TB Gold (QFT™)—in individuals currently taking, or being considered for, **immunosuppressive therapy** such as corticosteroids, DMARDS* and anti-tumor necrosis factor-alpha.

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 are thought to be due to reactivation of latent TB infection.[2,4,5] Studies have shown that patients taking steroid hormone therapy (e.g. dexamethasone, prednisolone) have greater than 5 times[1] increased risk of latent tuberculosis infection (LTBI) reactivation to active tuberculosis (TB), compared to the general population. For patients on anti-TNF-alpha therapy (e.g. infliximab, etanercept, adalimumab) there is a 4–8 fold increased risk.[2] Infliximab has been shown to increase the risk of TB in patients with rheumatoid arthritis from 6.2 cases to 52.5 cases per 100,000 patient-years of exposure.[3]

TB can be difficult to treat in patients who are treated with immunosuppressive agents such as anti-TNF-alpha, and the response to treatment can be unpredictable.[6] Of paramount concern is the occurrence of immune reconstitution syndrome in patients who have been treated with TNF-alpha blockers.[7,8] For these reasons screening for LTBI is advised for all patients before the use of TNF-alpha blockers.[9] This should include a careful history for *M. tuberculosis* exposure, a TST and a chest x-ray. Some authors have even advocated the use of two-step TST testing before the use of TNF-alpha blockers.[10]

In October 2001, the US Food and Drug Administration (FDA) modified infliximab labeling to include a warning about infliximab-associated TB that included instructions to screen for TB, treat LTBI before treatment and monitor for TB during infliximab therapy.[18]

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

The TST is widely used in the assessment of individuals with suspected TB—despite its well known limitations. A variety of factors—other than infection with *M. tuberculosis*—are known to induce a positive TST. 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. These false positive results can lead to unnecessary treatment of TB infection with possible detrimental side effects.

Studies have shown a high prevalence of anergy in the presence of immunosuppressive therapy.[11,12]

After the FDA warning about infliximab-associated TB, there were 130 reports received by the FDA (between 1 November 2001 and 30 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 (70%) patients had received a TST before the initiation of therapy. Of these patients, 34 (or approximately 75%) had a negative TST result.[19]

As the TST has limited sensitivity in patients who are already on immunosuppressive therapy, and false negative results do occur[7], a more accurate method of detecting TB infection is required.

*Disease modifying anti-rheumatic drugs

What is the correlation between QFT and *M. tuberculosis* exposure?

In a study involving individuals with chronic inflammatory rheumatic conditions who were taking immunosuppressive therapy*, it was found that in those patients with risk factors for latent TB—compared to patients without risk factors—the odds of a positive QFT was increased by a factor of 23.8. In comparison, the odds of a positive TST was increased by a factor of 2.8. The authors concluded "…the IFN-γ [QFT] assay was more closely associated with the presence of risk factors ($p = 0.009$), but less associated with BCG vaccination than the TST ($p = 0.025$)".[15]

* DMARDS, corticosteroids and/or TNF-alpha inhibitors

Due to the nature of the test, obtaining a TST result can take up to 72 hours. Is QFT any better?

QFT is a blood test, and results are generally available within 24 hours.

False negative TST results can occur in immunosuppressed individuals taking steroids and/or disease modifying anti-rheumatic drugs (DMARDS). How does QFT perform?

Studies have shown that QFT has excellent performance in immune suppressed patients taking steroids and/or DMARDS and that indeterminate QFT results occur infrequently (5-13%).[13,15,16,17] In indeterminate QFT subjects, the TST is generally negative[16] highlighting the need for care in interpreting a negative TST in those with potential immunosuppression.

An indeterminate QFT is meaningful, suggesting possible anergy, and does not indicate a failed test. By including an internal positive control (phytohemaglutinin tube), the QFT test enables the distinction between indeterminate tests and those that are truly QFT negative. The phytohemaglutinin positive control can be affected by blood mishandling, and should not be used as the sole assessment of immune status. In contrast, a negative TST does not differentiate between those individuals who are anergic and those who have a truly negative TST.

The TST is poor at detecting TB infection in individuals taking immunosuppressive therapy. Is QFT any better?

QFT has been shown to be more sensitive than the TST in immune suppressed patients (with chronic renal failure, diabetes mellitus, malignancies and taking immune suppressive therapy—78% vs. 50% respectively).[13] Unlike the TST, QFT is not subject to boosting, as it is not affected by prior BCG vaccination, and most non-tuberculous mycobacteria (except *M. marinum*, *M. szulgai* and *M. kansasii*).

The rapid proliferation of clinical information supporting the use of QFT has culminated in a recent recommendation by a panel of Swiss experts. This states that interferon-gamma release assays (such as QFT) should be used in place of the TST—for TB infection screening, prior to initiating anti-TNF-alpha therapy—as it is more accurate (sensitive and specific) than the TST in individuals with immune suppression.[14]

Summary of Published Studies

Publication	Main Finding
Beglinger C, Dudler J, Mottet C, Nicod L, Seibold F, Villiger P, Zellweger J. Screening for tuberculosis infection before the initiation of an anti-TNF-alpha therapy. *Swiss Med Wkly 2007; 137:620–2.*	Recommendation by Swiss experts to use interferon-gamma release assays (such as QFT) in place of the TST—for TB screening of patients prior to initiating anti-TNF-alpha therapy. In addition to QFT, screening should be based on a detailed medical history and a chest x-ray. The experts believe that cost-effectiveness of screening for latent infection with QFT instead of TST has been demonstrated.
Kobashi Y, Mouri K, Obase Y, Fukuda M, Miyashita N, Oka M. Clinical evaluation of QuantiFERON TB-2G test for immunocompromised patients. *Eur Resp J 2007; 30:945–50.*	Investigators compared QFT to the TST in 252 immunocompromised individuals (74 receiving immunosuppressive therapy) who were clinically suspected of having TB infection. The sensitivity of QFT in the 32 patients with culture-positive *M. tuberculosis* was 78% (25/32)—significantly higher than the TST sensitivity of 50.0% (16/32, $p < 0.05$).
Cobanoglu N, Ozcelik U, Kalyoncu U, Ozen S, Kiraz S, Gurcan N, Kaplan M, Dogru D, Yalcin E, Pekcan S, Kose M, Topaloglu R, Besbas N, Bakkaloglu A, Kiper N. 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.*	Investigators compared QFT to the TST for the diagnosis of LTBI in 38 healthcare worker controls and 68 patients with chronic inflammatory diseases (majority with either RA, AS or juvenile RA). All participants were BCG vaccinated, and 86.7% (59/69) of the patients with chronic inflammatory conditions were taking immunosuppressive therapy at the time of testing. In this study 10.3% (10/97) had a positive QFT result while 50.5% (49/97) were TST positive. To eliminate the effect of previous BCG vaccination, the authors divided the groups into 2 subgroups, subjects aged <25years and subjects aged ≥25years. Among 97 patients, 26 of 57 (45.6%) subjects aged <25 years were TST-positive, while only one was QFT positive—and 23 of 40 (57.7%) subjects aged ≥25 years were TST-positive while seven were QFT positive. The authors concluded "The high discordance, in subjects aged ≥25 years, between the TST and QFT Gold IT test may be due to repeated BCG vaccination. According to these results, of the 49 subjects who received INH prophylaxis against LTBI, it seems that only eight needed it". Of the 9/106 (8.5%) individuals with indeterminate QFT results, 6 were also TST negative and 7 were immunocompromised.
Matulis G, Jüni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases—performance of a Mycobacterium tuberculosis antigen specific IFN-gamma assay. *Ann Rheum Dis 2007 Sep 6 [Epub ahead of print].*	Investigators used QFT and TST to detect LTBI in 142 chronic arthritis patients (RA, AS or undifferentiated arthritis) the majority of whom were on immunosuppressive drugs-including TNF-alpha inhibitors. Positive QFT results were strongly correlated with risk factors for LTBI (more so than the TST). Positive TST results correlated with BCG vaccination status, however this was not observed with QFT. The incidence of indeterminate QFT results was low (6%) and this correlated with use of TNF-alpha inhibitors.
Pratt A, Nicholl K, Kay L. Use of the QuantiFERON TB Gold test as part of a screening programme in patients with RA under consideration for treatment with anti-TNF-alpha agents: the Newcastle (UK) experience. *Rheumatology 2007; 46:1035–6.*	Investigators reported their experience with QFT in 101 RA patients (78.5% of whom were BCG vaccinated) prior to commencing anti-TNF-alpha therapy. 6.9% of patients (7/101) were QFT positive, while 83% were QFT negative—which supports the higher specificity of QFT and that QFT is unaffected by BCG vaccination status. Only QFT-positive patients received INH prophylaxis. None of the 98 patients who finally received anti-TNF-alpha therapy subsequently developed TB.

Publication	Main Finding
Takahashi H, Shigehara K, Yamamoto M, Suzuki C, Naishiro Y, Tamura Y, Hirohashi Y, Satoh N, Shijubo N, Shinomura Y, Imai K. Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. *Rheumatol Int 2007; 27:1143–8.*	Investigators compared the effectiveness of QFT to conventional diagnostics methods (TST, imaging, and medical history) for diagnosing LTBI in 13 RA patients scheduled for—or undergoing—anti-TNF-alpha therapy. 7 patients were confirmed as LTBI positive by at least one method; and of these, 6 patients were QFT positive and 2 patients were detected as having LTBI based only on QFT. Only 5% of QFT results were indeterminate despite the use of anti-TNF-alpha therapy, methotrexate and corticosteroids.
Martinez LC, Harrison-Balestra C, Caeiro JP, Nousari CH. The role of the QuantiFERON-TB Gold test as screening prior to administration of tumour necrosis factor inhibitors. *Arch Dermatol 2007; 143:809–10.*	Case reports on the use of QFT in 2 patients with psoriasis. Both patients had negative QFT and TST results as well as a normal chest x-ray. Both received anti-TNF-alpha therapy with improvement of their psoriasis and no evidence of TB.
Ravn P, Munk ME, Andersen AB, Lundgren B, Nielsen LN, Lillebaek T, Soerensen IJ, Andersen P, Weldingh K. Reactivation of tuberculosis during immunosuppressive treatment in a patient with a positive QuantiFERON-RD1 test. *Scand J Infect Dis 2004; 36:499–501.*	Case report of a patient with polymyositis who developed active tuberculosis during immunosuppressive treatment. TST and chest x-ray failed to demonstrate LTBI, whereas a blood sample—that was tested with a modified QFT assay—was positive, indicating that this patient was latently infected before starting immunosuppressive therapy.
Arend SM, Leyten EM, Franken WP, Huisman EM, van Dissel JT. A patient with de novo tuberculosis during anti-tumor necrosis factor-alpha therapy illustrating diagnostic pitfalls and paradoxical response to treatment. *Clin Infect Dis 2007; 45:1470–5.*	Case report of a patient with Crohn's disease who was exposed to an individual with smear-positive TB while receiving infliximab treatment. The patient developed fever, dry cough and experienced weight loss. Despite having normal chest x-ray and negative TST results—similar to those obtained when initially screened for LTBI prior to the initiation of infliximab—their QFT result was positive. Acid-fast staining and polymerase chain reaction of bronchoalveolar lavage fluid samples returned negative results, but *M. tuberculosis* was subsequently cultured. After the initiation of 4 antitubercular drugs and the discontinuation of infliximab therapy, the patient developed immune reconstitution syndrome.
Efthimiou P, Sood S. Quantiferon TB Gold Test: the new standard for screening of latent tuberculosis in patients with rheumatoid arthritis? *Ann Rheum Dis 2007; 66:276.*	Report outlining experience with QFT in 2 RA patients who were candidates for anti-TNF-alpha treatment. Both patients were screened for LTBI using the TST, chest x-ray and QFT. Both patients had negative TST results; however both had positive QFT results and one of the patients had a chest x-ray consistent with a past history of primary TB. Both patients were given a 9-month course of isoniazid / vitamin B6.

QFT™
QuantiFERON-TB Gold

References

1. Cisneros JR, Murray KM. Corticosteroids in tuberculosis. *Ann Pharmacother 1996; 30:1298–303.*
2. Winthrop KL, Siegel JN, Jereb J, Taylor Z, Iademarco MF. Tuberculosis associated with therapy against tumor necrosis factor alpha. *Arthritis Rheum 2005; 52:2968–74.*
3. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum 2004; 50:372–9.*
4. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis 2004; 38:1261–5.*
5. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. 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.*
6. Garcia Vidal C, Rodríguez Fernández S, Martínez Lacasa J, Salavert M, Vidal R, Rodríguez Carballeira M, Garau J. Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. *Clin Infect Dis 2005; 40:756–9.*
7. Arend SM, Leyten EM, Franken WP, Huisman EM, van Dissel JT. A patient with de novo tuberculosis during anti-tumor necrosis factor-alpha therapy illustrating diagnostic pitfalls and paradoxical response to treatment. *Clin Infect Dis 2007; 45:1470–5.*
8. Belknap R, Reves R, Burman W. Immune reconstitution to Mycobacterium tuberculosis after discontinuing infliximab. *Int J Tuberc Lung Dis 2005; 9:1057–8.*
9. Long R, Gardam M. Tumour necrosis factor-alpha inhibitors and the reactivation of latent tuberculosis infection. *CMAJ 2003; 168:1153–6.*
10. Gómez-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: 756–61.*
11. Mow WS, Abreu-Martin MT, Papadakis KA, Pitchon HE, Targan SR, Vasiliauskas EA. High incidence of anergy in inflammatory bowel disease patients limits the usefulness of PPD screening before infliximab therapy. *Clin Gastroenterol Hepatol. 2004; 2:309–13.*
12. Ponce de León D, Acevedo-Vásquez E, Sánchez-Torres A, Cucho M, Alfaro J, Perich R, Pastor C, Harrison J, Sánchez-Schwartz C. 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.*
13. Kobashi Y, Mouri K, Obase Y, Fukuda M, Miyashita N, Oka M. Clinical evaluation of QuantiFERON TB-2G test for immunocompromised patients. *Eur Resp J 2007; 30:945–50.*
14. Beglinger C, Dudler J, Mottet C, Nicod L, Seibold F, Villiger P, Zellweger J. Screening for tuberculosis infection before the initiation of an anti-TNF-alpha therapy. *Swiss Med Wkly 2007; 137:620–2.*
15. Matulis G, Jüni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases - performance of a Mycobacterium tuberculosis antigen specific IFN-gamma assay. *Ann Rheum Dis 2007 Sep 6 [Epub ahead of print].*
16. Cobanoglu N, Ozcelik U, Kalyoncu U, Ozen S, Kiraz S, Gurcan N, Kaplan M, Dogru D, Yalcin E, Pekcan S, Kose M, Topaloglu R, Besbas N, Bakkaloglu A, Kiper N. 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.*
17. Takahashi H, Shigehara K, Yamamoto M, Suzuki C, Naishiro Y, Tamura Y, Hirohashi Y, Satoh N, Shijubo N, Shinomura Y, Imai K. Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. *Rheumatol Int 2007; 27:1143–8.*
18. Remicade [product label]. *Accessed at http://www.fda.gov/medwatch/safety/2006/Oct_PIs/Remicade_PI.pdf on 10th December 2007.*
19. Raval A, Akhavan-Toyserkani G, Brinker A, Avigan M. Brief Communication: characteristics of spontaneous cases of tuberculosis associated with infliximab. *Ann Intern Med 2007; 147:699–702.*

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

North America / South America
Cellestis Inc.
Email: customer.service@cellestis.com
Fax: +1 661 775 7479
Tel: +1 661 775 7480 (outside USA)
Toll free: 800 519 4627 (USA only)

Europe / Middle East / Africa
Cellestis GmbH
Email: europe@cellestis.com
Fax: +49 6151 428 59 110
Tel: +49 6151 428 59 0

Asia / Oceania
Cellestis International
Email: quantiferon@cellestis.com
Fax: +61 3 9571 3544
Tel: +61 3 9571 3500

L05995023A