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Clinical Study

The Performance of Quantiferon TB Gold In-Tube as a Screening Tool in Paediatric Rheumatology prior to Initiation of Infliximab: A Single Centre's Experience

Despoina Maritsi,[1,2] Muthana Al-Obadi,[1] Paul A. Brogan,[1] Despina Eleftheriou,[1] and Garth L. J. Dixon[1]

[1] *Academic Department of Paediatric and Adolescent Rheumatology, Great Ormond Street Hospital and Institute of Child Health, London WC1N 3JH, UK*
[2] *Rheumatology Department, Great Ormond Street Hospital NHS Trust, Great Ormond Street, London WC1N 3JH, UK*

Correspondence should be addressed to Despoina Maritsi, dmaritsi@yahoo.co.uk

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Background. Patients with autoimmune diseases and latent tuberculosis infection (LTBI) are at risk of developing catastrophic tuberculosis disease following infliximab treatment. Quantiferon-TB gold in-Tube (QTB) has proven a more accurate screening tool than tuberculin skin test (TST) in adult populations. *Objectives*. To assess the utility and validity of QTB in children, prior to treatment with infliximab. *Methods*. Retrospective cohort of patients started on infliximab following endorsement of QTB as a screening tool by the NICE guidelines in 2006. *Results*. Twenty three patients (12 females and 11 males) were included in the study. A chest radiograph (CXR) and QTB was performed prior to starting infliximab. Fourteen patients had a recorded negative TST result. One patient had a positive QTB while two had indeterminate results. Their CXRs were not suggestive of TB and TSTs were negative. The patients with indeterminate results were started on infliximab and had regular clinical assessment for TB disease. Repeat QTB was negative in one while remained indeterminate in the other. None of our 23 patients developed TB. *Conclusion*. QTB is a useful screen tool for LTBI. Indeterminate results warrant careful assessment and re-evaluation, but should not preclude from initiation of anti TNF treatment.

1. Background

Antitumor Necrosis Factor alpha (TNFα) agents are a rapidly developing field of medicines in pediatric rheumatology. Recent papers have presented the efficacy and effectiveness of anti-TNFα therapy in disease control and improvement in quality of life. Agents commonly used include infliximab, an anti-TNFα chimeric monoclonal antibody, etanercept, an anti-TNFα receptor fusion IgG protein, and adalimumab, a humanized monoclonal antibody acting as TNFα receptor blocker. However, initiation of anti-TNFα treatment is not without risk. TNF is released by macrophages and is a potent regulator for granuloma formation and limitation of the mycobacterium tuberculosis (TB) infection. Anti-TNFα medications suppress TNF actions and inhibit its restrictive role in controlling TB, thus potentially leading to reactivation of TB disease in those with LTBI. This may have catastrophic consequences especially in patients with an already dysregulated and compromised immune system [1]. A tool that could rule out TB infection prior to anti-TNFα medications is therefore highly desirable.

Over the last three years the use of Interferon gamma releasing assays (IGRAs) has been increasingly introduced in order to verify or rule out latent TB infection (LTBI) [2]. There are voluminous data in the medical literature proving the superiority of QTB and Elispot in the diagnosis of latent TB infection in cases where previous methods applied such as tuberculin skin tests (TSTs) have failed. IGRAs are now considered sensitive and specific tools which assist us to differentiate between latent infection, infection from atypical

mycobacteria, and in cases of previous BCG vaccination. It is found to be significantly more sensitive in detecting LTBI especially in immunocompromised patients. However, there are no current data to support its use in children with multisystemic autoimmune diseases.

In the UK the use of IGRA as a screen tool to rule out LTBI was implemented in National Institute of Clinical Excellence (NICE) guidelines in March 2006 while its use prior to commencement of anti-TNFα treatment was established in 2007.

2. Aim

Our aim is to describe the findings of QTB test when applied to a paediatric rheumatology population and to assess the efficacy of this test versus the methods previously used for the exclusion of TB infection prior to starting anti-TNFα treatment.

3. Setting

The setting is a quarterly Paediatric Rheumatology Centre in the UK caring for all types of rheumatic diseases. In our hospital QTB was the IGRA of choice used and it became available in clinical practice in 2005 while the Rheumatology Team routinely inaugurated QTB to rule out LTBI in 2007.

4. Methods

We have retrospective case study of all patients on infliximab (the protean anti-TNFα medication used) since 2007 and their risk assessment for TB infection prior to beginning of treatment. Patients' data were collected using the hospital's electronic medical data system, systemic review of medical records, review of patients' vaccination records (red book), and personal communication with responsible physician.

5. Analysis

Data were collected regarding age, gender, race, diagnosis, previous tuberculin skin tests (TSTs) and BCG status, risk assessment for TB, as well as previous treatment received. Twenty seven patients had started infliximab treatment since 2007. In four of these patients there was no record of the QTB test. The remaining 23 patients (12 females, 11 males) had QTB and CXR results recorded. QTB results were reported as positive, negative, or indeterminate according to manufacturers (Cellestis Corp. Australia) instructions using their proprietary software. Median age was 8.9 years (range from 1.5 to 13 years). Thirteen (55%) patients were Caucasian, 19% were Afro-Caribbean, and the remaining were of Asian origin. Their underlying diagnoses were from wide spectrum of autoimmune diseases including juvenile idiopathic arthritis (JIA) 34%, uveitis 5%, juvenile dermatomyositis 26%, vasculitis 9%, systemic onset JIA 17%, and inflammatory bowel disease 9%. Five (22%) patients were on methotrexate, and the remaining were on both medications for over six months prior to performing the test. Lymphocyte count was recorded at the time of QTB performance and was within normal limits for all patients (mean: 2.79/mm^3; range: 1.59–4.5/mm^3; reference range: 1.5–5.0/mm^3). Fourteen (61%) patients had a previous record of a negative TST. Three (13%) patients were considered high risk, while the remaining were considered low risk for LTBI. TB risk evaluation was performed using the questionnaire formulated by the United States Pediatric Tuberculosis Collaborative Group, which was published in 2004 [3].

Table 1: Showing cumulative results.

Test/Results	Positive	Indeterminate	Negative	Not recorded
QTB	1 (4.3%)	2 (8.7%)	20 (87%)	—
CXR	0	0	23 (100%)	0
TST	0	0	14 (61%)	9 (39%)
BCG	5 (22%) (scar present)	—	—	18 (78%)
Risk assessment	3 (13%) (high)	—	20 (87%) (low)	0

None of the patients had a positive TST or a chest radiograph suggestive of TB. Five (22%) patients had a BCG scar. Twenty (87%) patients had a negative QTB test; two (8.7%) had an indeterminate result; one (4.3%) has a positive test (see Table 1). None of these three patients belonged to the young age group, none had abnormal findings on their CXR, and the sputum cultures were negative on several occasions. The patient with positive QTB, who belonged to the high-risk group for TB, received six-month anti-TB treatment following which QTB has become negative. The patients with indeterminate results were low risk for LTBI; a repeat QTB test was negative in one while remained indeterminate in the other. The former event may be attributed to an improved technique used the second time. There were no unifying data between the patients with the indeterminate results and their lymphocyte count was normal. Elispot was unavailable for cross checking. All 23 patients have been treated with infliximab. The mean dose was 6 mg/kg/dose and mean dose intervals 6.5 weeks (range from 4 to 9 weeks). Mean duration of treatment was 13 months (range 3–24 months). Early withdrawal of infliximab was due to treatment failure (failure to control the disease). None of our 23 patients has developed TB.

6. Discussion

Previous studies have enlightened the difference in specificity and sensitivity of IGRA versus tuberculin skin testing in immune competent children. Additionally, studies performed on adult populations with underlying autoimmune conditions proved the superiority of QTB over TST to various degrees [4, 5]. The literature however is limited to case reports when it comes to children on anti-TNFα and risk of TB infection [6], and since immune dysregulation and autoimmune mechanisms differ, results based on adult studies cannot be extrapolated directly on the paediatric

population. Our study is in agreement with previous studies showing the inconsistency between TST and QTB tests. Although our data are not numerically sufficient to prove statistical significance, given the rarity of autoimmune diseases in the paediatric population, there are significant clinical data to support the use of QTB as a valuable assessment tool for exclusion of TB. Interestingly, even in patients with known history of BCG vaccination TSTs were not recorded as positive. Negative TST results may be attributed to a combination of factors such as concurrent or recent use of steroids and/or defective delayed type response to tuberculin. The fact that this is a retrospective study may explain why 9 (39%) of our patients did not have a TST test, since it was felt that QTB is a superior method to exclude LTBI. Positive QTB results should be regarded as true even in the absence of symptoms or radiological findings. Our yield of indeterminate results was lower than what is mentioned in the literature (8.7% versus 21%). Indeterminate results should be treated cautiously; patients require physical examination and risk assessment for LTBI. A recently published study from the same institution proved that young age and immunosuppression are two independent risk factors for an indeterminate result [7].

In our cohort, none of the patients who belonged to the young age group had an indeterminate result irrespectively of underlying diagnosis or previous treatment received. As these patients were low risk for TB infection and the rest of the tests performed were negative, we proceeded with the infliximab. None of our patients has developed TB disease. There are limitations in our study mainly due to the small number of patients and the limited follow-up period. Previous studies based on adults have shown that TB reactivation occurs within the first 12 weeks after initiation of treatment and it could be argued that a mean duration of 13 months is not a safe time frame [8]. However the minimal duration of treatment was three months (12 weeks) which is the average expected time for TB disease to flare up.

7. Conclusion

Positive IGRAs should be viewed as evidence that exposure to mycobacterium TB has occurred and careful clinical history and investigations including CXR are required to rule out active disease. In absence of any evidence of active disease, careful risk assessment for LTBI must guide further decisions on treatment.

In general, QTB is a relatively safe and effective method to screen for LTBI. The lack of a gold standard other than the development of TB disease is missing which makes validation of these tests very difficult. Randomized control trials would be required to ascertain this issue and there is a study currently undertaken in adults with rheumatoid arthritis and positive QTB who are given infliximab without prior anti TB treatment. Nonetheless, such studies would be hazardous to perform in children bearing in mind the difficulties in proving TB infection as well as the risks associated with reactivation or primary progression of TB while immunosupressed, and it would be highly unlikely to meet standards of ethical approval. However, larger studies are required and adverse events of TB disease whilst on anti-TNFα treatment need to be reported.

Key Points

(i) A negative TST in children receiving immunosuppressive treatment is not adequate in excluding LTBI.

(ii) Indeterminate QTB results should be viewed cautiously; however they should not compromise the treatment of the underlying condition.

Conflicts of Interests

The authors declare that there is no conflict of interests.

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References

[1] D. P. de León, E. Acevedo-Vásquez, A. Sánchez-Torres et al., "Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis," *Annals of the Rheumatic Diseases*, vol. 64, no. 9, pp. 1360–1361, 2005.

[2] G. Ferrara, M. Losi, R. D'Amico et al., "Use in routine clinical practice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study," *The Lancet*, vol. 367, no. 9519, pp. 1328–1334, 2006.

[3] L. Saiman and P. Colson, "Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents," *Pediatrics*, vol. 114, no. 4, pp. 1175–1201, 2004.

[4] I. Brock, M. Ruhwald, B. Lundgren, H. Westh, L. R. Mathiesen, and P. Ravn, "Latent tuberculosis in HIV positive, diagnosed by the *M. tuberculosis* specific interferon-γ test," *Respiratory Research*, vol. 7, article 56, 2006.

[5] A. Pratt, K. Nicholl, and L. Kay, "Use of the QuantiFERON TB Gold test as part of a screening programme in patients with RA under consideration for treatment with anti-TNF-α agents: the Newcastle (UK) experience," *Rheumatology*, vol. 46, no. 6, pp. 1035–1036, 2007.

[6] L. Assante, M. Bocchino, M. Alessio, R. Ambrosi, A. Sanduzzi, and A. Guarino, "Performance of IFN-gamma release assays for detection of tuberculosis infection in JIA children on biological therapy," *Pediatric Rheumatology*, vol. 6, supplement 1, p. 60, 2008.

[7] T. Haustein, D. A. Ridout, J. C. Hartley et al., "The likelihood of an indeterminate test result from a whole-blood interferon-γ release assay for the diagnosis of *Mycobacterium tuberculosis* infection in children correlates with age and immune status," *Pediatric Infectious Disease Journal*, vol. 28, no. 8, pp. 669–673, 2009.

[8] R. S. Wallis, M. S. Broder, J. Y. Wong, M. E. Hanson, and D. O. Beenhouwer, "Granulomatous infectious diseases associated with tumour necrosis factor anatagonists: correction," *Clinical Infectious Diseases*, vol. 38, no. 9, pp. 1261–1265, 2004.