Review Article

The role of interferon gamma release assays in the monitoring of response to anti-tuberculosis treatment in children

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EDUCATIONAL AIMS

- To describe the potential role of IGRAs as markers of response to anti-TB treatment in children
- To illustrate the strengths and weaknesses of the IGRAs as diagnostic and surrogate markers of TB in children
- Toemphasise the importance of developing objective biomarkers of response to anti-TB treatment in children

ARTICLE INFO

SUMMARY

Successful control of childhood TB requires early diagnosis, effective chemotherapy and a method of evaluating the response to therapy. Identification of suitable biomarkers that predict the response to anti-TB therapy may allow the duration of treatment to be shortened. The majority of biomarker studies in paediatric TB have focused on the role of T cell-based interferon-gamma (IFN-γ) release assays (IGRAs) in the diagnosis of either latent or active disease. Little has been published on the role of IGRAs in the monitoring response to therapy in children. We reviewed the available literature to ascertain the value of IGRAs in the monitoring of response to anti-TB therapy in children. We explored the results of the few studies that have investigated the role of IGRAs as markers of response to anti-TB treatment in children. We conclude that the role of IGRAs as surrogate markers appears promising. Robust clinical trials are, however, needed to entrench the value of IGRAs as surrogate biomarkers of response to anti-TB therapy in children.

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INTRODUCTION

Tuberculosis (TB) was declared a global health emergency by the World Health Organisation (WHO) almost two decades ago [1]. The recently published WHO Roadmap for childhood tuberculosis has emphasised the continuing urgency of the problem in children [2], yet little progress has been made in reversing the trends of the escalating TB epidemic. There are several reasons for this tragic situation viz. the difficulty in confirming a diagnosis of TB in children, the prolonged duration of therapy with the consequent lack of adherence, the lack of robust drug sensitivity assays to ensure effective therapy, the emergence of major outbreaks of TB in HIV-infected adults who act as reservoirs that continually infect and re-infect children and the lack of robust markers to determine response to therapy in children who have empiric therapy initiated on suspicion of the diagnosis [3]. The response to anti-TB treatment in children is largely determined through clinical and radiographic changes and occasionally through mycobacterial clearance at the end of treatment. Most children are treated with anti-TB therapy on scant clinical and laboratory grounds in an effort to prevent the harm associated with a missed diagnosis, yet the burden to the healthcare system associated with this practice is substantial as therapy is prolonged [4]. The current treatment interval of 6 months for children with pulmonary TB, between 18 and 24 months for multidrug-resistant (MDR) and possibly longer for extensively drug-resistant (XDR) TB contributes to the failure of management strategies due to poor patient adherence [5].

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Table 1
The reported sensitivity and specificity of IGRAs and TST for the diagnosis of LTBI

Test	Sensitivity (%)	Specificity (%)
QFT-GIT	83	91
T.SPOT.TB	84	94
TST	84	88

Data from Hesseling and Mandalakas (2000) [15].

Moreover, the evidence for these currently recommended treatment durations is uncertain in children. Furthermore, the presence of HIV co-infection poses additional challenges as to the optimal timing of initiation and duration of anti-TB therapy given the associated adverse effects and drug-drug interactions with a high pill burden [6].

It is, therefore, essential to improve the diagnostics associated with childhood TB. In addition, there is an urgent need to evaluate the role of biomarkers that will allow specific recognition of response to anti-TB therapy.

What is known about IGRAs in the diagnosis of LTBI and active TB disease?

The tuberculin skin test (TST) has been widely used in the diagnosis of paediatric TB, [7] but it has been associated with false positive and negative results in HIV-infected, malnourished children, and in individuals exposed to non-tuberculous mycobacteria (NTM) [8–13]. Its inability to distinguish between latent TB infection (LTBI) and active TB hampers its use [14,15]. The limitations of the TST have led to the development of T-cell-based interferon-gamma (IFN-γ) release assays (IGRAs) viz. the commercially-based QuantiFERON-TB Gold *In Tube* (QFT-GIT) assay and the pre-commercial T.SPOT.*TB* in the diagnosis of LTBI and active disease in children. Current knowledge can be summarised as:

- IGRAs cannot differentiate between LTBI and active TB disease [16].
- The sensitivity and specificity of IGRAs and TST for the diagnosis of LTBI as reported in a meta-analysis and systematic review [16] is shown in Table 1. Therefore, the current evidence suggests that IGRAs do not replace TST for the diagnosis of LTBI.
- The specificity and sensitivity of IGRAs in the diagnosis of LTBI and active TB disease may be influenced by the burden of TB [17] (Table 2). Several factors could account for the observed difference in the sensitivity and specificity of IGRAs in low burden versus high burden settings. These include HIV infection, helminth infections, excessive exposure to *Mycobacterium tuberculosis* (MTB), malnutrition, exposure to NTM and transmission dynamics [18].
- A combination of TST and an IGRA increases the sensitivity for the diagnosis of active TB (reported to be 91%) compared to IGRA alone [19,20]. Further robust studies are, however, required to confirm this observation in the clinical setting especially in high burden areas.

Rationale for the review

The role of IGRAs in the diagnosis of LTBI and active disease in children has been presented in several published works. Emerging

Table 2
The effect of the burden of TB disease on the sensitivity and specificity of IGRAs

	Low burden TB setting	High burden TB setting
LTBI	More specific than TST	Low sensitivity
Active disease	Higher sensitivity	Low sensitivity and specificity

Summarized from Machingaidze et al. (2011) [16].

data from a few recent studies, however, suggest a potential role for IGRAs as markers of response to anti-TB treatment. To the authors' knowledge, this is the first review to examine the available literature on the role of IGRAs in the monitoring of response to anti-TB treatment in children.

METHOD

Published articles on the role of IGRAs in the diagnosis and monitoring the response of treatment in both adult and paediatric TB were searched in the data bases of Pubmed, ScienceDirect, Scirus, and unboundmedicine.com. Key words entered included "interferon gamma release assays", "tuberculosis", "diagnosis", "adult", "paediatric", "children" and "monitoring response to treatment". A summary of studies that have investigated the usefulness of IGRAs as markers of response to anti-TB treatment is presented in Table 3.

Interpretation of the Results

It is postulated that the IFN-γ response is related to the mycobacterium load. This is supported by the findings of the majority of studies who showed a decrease in IFN-γ following induction with anti-TB treatment [22–25,27,28]. There was also a decrease in IFN-γ induction in response to anti-TB treatment in nearly 80% of culture-confirmed TB cases. [25] However, the usefulness of these tests in predicting relapse cases or recurrent disease was not available. Two studies did report an increase in IFN-γ responses following 2 to 6 months of anti-TB therapy in adults and children [21,26]. These apparently conflicting findings may be explained by two opposing hypotheses. One proposes that treatment of TB would enhance immune function leading to increased IFN-γ production by T-cells in a response to control infection and which later decreases [29]. An alternate hypothesis states that the specific antigen burden is decreased during anti-TB treatment which reduces the frequency of circulating antigen-specific T-cells [27]. It is also postulated that an increasing ESAT-6 specific T-cell pool that is not directly associated with immunity during anti-TB treatment could account for the increased T-cell responses to ESAT-6 in patients who were treated [19].

Nicol et al. [24] caution against using the initial decrease in ELISPOT responses as a reliable marker of response to anti-TB treatment in children as they observed an initial increase in IFN-γ responses after 1 month of anti-TB therapy. A decrease in responses was then observed at 3 and 6 months after commencing therapy, but the levels were similar to those seen at baseline. This observation may be explained by the following possible reasons. During initiation of anti-TB treatment, there is an increase in initial antigen presentation due to the eradication of the pathogen leading to T-cell responses that increase during initial treatment and decrease as the MTB load declines [25]. Patients with active disease are usually unwell and have depressed T-cell responses and the IFN-γ signalling may be affected directly by MTB [26–30]. Overall, an increase in IFN-γ response after 10 days of anti-TB treatment followed by a decrease in the magnitude of IFN-γ response was observed in children following completion of anti-TB treatment [26]. This finding highlights the potential value of IGRAs in identifying newly acquired infection and to detect low numbers of replicating mycobacteria [26].

The first study to describe the IFN-γ responses to anti-TB treatment in HIV co-infected children reported a significant decrease in the magnitude of the IFN-γ response to individual and combined MTB-specific antigens in TB/HIV co-infected children [28]. The authors, however, questioned the clinical usefulness of the IGRA as a surrogate marker of response to anti-TB treatment as nearly half the children had a positive IFN-γ