Editorial

Could IFN-γ levels in serial QuantiFERON predict tuberculosis development in young children?

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Comment on: Andrews JR, Nemes E, Tameris M, *et al.* Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study. Lancet Respir Med 2017;5:282-90.

Received: 17 September 2017; Accepted: 16 October 2017; Published: 08 November 2017.

doi: 10.21037/jlpm.2017.10.06

View this article at: http://dx.doi.org/10.21037/jlpm.2017.10.06

Tuberculosis (TB) is an infectious disease of important global health concern. On 2016, TB caused 10.4 million new cases and 1.8 million deaths (1). Compared to adults, young children infected with *Mycobacterium tuberculosis* (*M.TB*) are at high risk of progression and have an increased risk of developing a severe TB outcome (2). TB screening recommendations in children and other risk groups are described in several international and national guidelines, as well as the recommended prophylaxis (3,4). However, in some cases, prophylaxis may turn out to be unnecessary and depending on the setting it may be impossible to access. In order to better characterize who would benefit from prophylaxis, there is a need to identify those at a higher risk of developing active TB.

Interferon gamma (IFN-γ) release assays (IGRAs) are diagnostic tests used for TB infection detection. IGRAs are based on IFN-γ detection released by T-cells after whole blood stimulation with specific *M.TB* complex antigens. Currently there are two IGRAs available: QuantiFERON Gold in-Tube (QFN-G-IT) and T-SPOT.TB, both based on an enzyme-linked immunosorbent assay. QFN-G-IT detects the amount of IFN-γ released by T-cells, whereas the T-SPOT.TB detects the number of IFN-γ producing cells. Recently, a new version of the QFN-G-IT, the QFN-Plus, has been introduced (5,6). This assay detects the IFN-γ produced by CD4 and also by CD4 and CD8 together. IGRAs have been extensively studied (7-11) and, although they have a good negative predictive value, they have a poor positive predictive value: 2.7% overall or 6.8% in high risk groups according to Diel *et al.* (9), and up to 17% according to Altet *et al.* (10), which represents an issue for prophylaxis prescription.

Several studies have assessed the amount of IFN-γ released in QFN-G-IT test at baseline, conversions and also reversions, in order to find a relation between concentrations and risk of progression, instead of focusing only on positive or negative test results (10,12-17). However, findings in this regard are conflicting and more needs to be done to assess the potential role of different IFN-γ concentrations in future TB development.

Andrews *et al.* (18) recently addressed this issue in young children studying the relation between IFN-γ in QFN-G-IT conversions and risk of TB development, and QFN-G-IT reversions. The authors included 2,512 South African young children aged 4–6 months, BCG vaccinated on the first week after birth, HIV negative, with no known TB contact and a negative QFN-G-IT (<0.35 IU/mL) at the beginning of the study. The study subjects were part of a MVA85A vaccine trial (19). However, since the vaccine did not seem to have any effect, every subject was considered in the study regardless the group they were initially divided into (placebo group, with *Candida* spp., and MVA85A vaccinated). Subjects underwent a second QFN-G-IT test 336 days after the first one, and a third one when the patient developed active TB (6–24 months after the first 336 days) or at the end of the study (October 2012). Every patient was followed-up every 3 months in order to check for active TB exposure and symptoms.

According to IFN-γ levels, patients were divided in three groups: (I) under 0.35 IU/mL, (II) between 0.35 and 4.00 IU/mL, and (III) above 4.00 IU/mL. After the second QFN-G-IT test, 7% (172/2,512) of the patients had a positive result. From the 172 converters at day 336, 79 (46%) had IFN-γ levels between 0.35 and 4.00 IU/mL and only 2 (2.5%) patients developed active TB. A 36.6% (63/172) of the converters had IFN-γ levels above 4.00 IU/mL and 15.9% (10/63) were diagnosed with TB. When comparing with non-converters and converters at day 336 with IFN-γ values under 4.00 IU/mL, the authors found that TB incidence in converters was significantly higher when IFN-γ values were above 4.00 IU/mL. Regarding the patients with a negative QFN-G-IT test at day 336, 16 developed active TB, from which 14 were tested and QFN-G-IT positive at the diagnostic moment. Regarding reversions, 91 out of the 172 patients who had a QFN-G-IT conversion at day 336 were retested and 53 (58%) reverted to a negative result. The authors found that there were significantly more reversions in converters with IFN-γ levels below 4.00 IU/mL.

To date, many studies have been performed in the assessment of IGRAs and TB risk (7,10,20). However, studies that consider TB disease progression focusing not only on positive and negative result but also on IFN-γ levels at baseline, conversions and reversions are not abundant.

In 2002, Doherty *et al.* described a strong association between IFN-γ production and TB progression, in Ethiopian contacts after a 5-day PBMCs stimulation with ESAT-6 (13). The authors found that contacts who progressed to active TB were the ones with the highest IFN-γ levels (P<0.001). Similarly, in their contact tracing study in household contacts, del Corral *et al.* described a significant trend for TB development in high IFN-γ producers after CFP-10 stimulation (21). Pai *et al.* found that healthcare workers with tuberculin skin test (TST) and QFN-G-IT positive had high IFN-γ levels and were less likely to revert, being reversions more frequent in those individuals with IFN-γ levels close to 0.35 IU/mL and considering that conversions with high IFN-γ levels might predict TB progression (14). Moreover, it has been described that adolescents with a recent QFN-G-IT conversion have a higher risk of TB progression (17).

In a previous study, we assessed the risk of TB development based on QFN-G-IT and TST in contacts (adults and children) with both positive and negative QFN-G-IT results at baseline (10). Overall, we described a higher risk of developing active TB disease in the first 2 years after infection in those contacts with a positive QFN-G-IT test. Focusing on children, all of those who progressed to TB had, at baseline, IFN-γ levels above 0.35 IU/mL. Moreover we found that TB progression risk was higher in contacts with initial IFN-γ levels above the limit of detection (10 IU/mL).

Similarly, Diel *et al.* compared TST and QFN-G-IT in contacts (both adults and children), and evaluated progression to TB during a 4-year follow-up period (12). From the overall study population, the majority of cases with positive QFN-G-IT who developed TB had IFN-γ levels 10-fold higher than the cut-off (0.35 IU/mL), and the majority had IFN-γ levels above the limit of detection. Regarding the children cohort alone, 6 out of the 21 untreated patients with positive QFN-G-IT developed active TB during the follow up and had high IFN-γ levels: five of them with more than 4.00 IU/ml and one 3.59 IU/mL. In this study, all children with positive QFN-G-IT who did not develop active TB had responses lower than 4.5 IU/mL.

Studies developed so far show the importance of considering QFT-G-IT results not only as dichotomous (positive or negative) but also as quantitative. Results and study population vary among studies. However, overall, they seem to relate high IFN-γ levels to TB progression and low IFN-γ levels with low reversion risk. Therefore, Andrews *et al.* study has an increase value in this matter: it is a prospective study with a good follow-up period, the study population is entirely integrated by young children with negative QFN-G-IT at baseline, and the population is well described. In this study authors conclude that (I) TB incidence is significantly higher in children converters with more than 4.00 IU/mL of IFN-γ; (II) converters with IFN-γ values under 4.00 IU/mL have an increased risk of reversion. These results suggest that monitoring in young children could serve to make better decisions in prophylaxis prescription considering especially those with >4.00 IU/mL conversions.

Although these results are promising it should be taken into account that (I) even though contacts with higher IFN-γ levels are the ones who progress to active TB, there is an overlap with those positive QFN-G-IT contacts who remain healthy, and (II) although the risk of TB progression rises with high IFN-γ levels, there are also contacts who develop active TB and have low initial IFN-γ levels (10,12,22). Regarding IFN-γ levels differences in children among latent TB infection (LTBI) and active TB groups, there is no clear association. Whittaker *et al.* (23) described

a lower amount of IFN-γ in LTBI patients compared to active TB, whereas Latorre *et al.* described no significant difference between these two groups (22). In addition to these concerns, Kampmann *et al.* stated that a negative IGRA should not exclude active TB in children but rather serve to confirm it (24). Furthermore, the fact that IFN-γ levels have been described as highly variable in serial IGRA testing (25) should be taken into account and assessed in further studies in this same age cohort before changing the actual guidelines.

Altogether, high IFN-γ conversion levels could serve as indicators for TB progression in the study population, enabling better diagnosis and chemotherapy decisions. However, as the authors state, these findings should be further evaluated in order to consider a revision of the international guidelines in the use of IGRAs in children especially given the IFN-γ previously described variability.

Acknowledgments

Funding: This study was supported by grants from: the Instituto de Salud Carlos III (PI/16/01912), integrated in the Plan Nacional de I+D+I and co-funded by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER), and CERCA Programme/Generalitat de Catalunya. J Domínguez is a researcher from the Miguel Servet programme.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by Section Editor Maoshui Wang (Department of Lab Medicine, Shandong Provincial Chest Hospital, Jinan, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2017.10.06). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jlpm.2017.10.06
Cite this article as: Villar-Hernández R, Latorre I, Altet N, Domínguez J. Could IFN-γ levels in serial QuantiFERON predict tuberculosis development in young children? J Lab Precis Med 2017;2:86.

