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Original Article

QuantiFERON-TB Gold Plus for screening and monitoring latent tuberculosis infection in spondyloarthritis patients

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Abstract

Introduction: The optimal frequency of rescreening for latent tuberculosis infection (LTBI) in patients with inflammatory arthritis on biologic/targeted-synthetic disease modifying anti-rheumatic drugs (b/ts-DMARDs) is uncertain. We aimed to evaluate the impact of LTBI re-screening using the QuantiFERON-TB Gold Plus (QFT-Plus; QIAGEN, Germantown, USA) test method and to assess the frequency of re-screening in real-life spondyloarthritis (SpA) patients on b/ts-DMARDs.

Methodology: This study focused on patients with SpA who were scheduled for b/ts-DMARDs therapy and underwent QFT-Plus testing to screen for LTBI. The study analyzed whether QFT-Plus test negative patients underwent sequential QFT-Plus tests during follow-up and the timing of these tests. Cases of tuberculosis (TB) reactivation were documented, and the clinical status of affected patients were recorded.

Results: Of the 801 patients included in the study, the QFT-Plus tests were negative in 701 (87.5%), positive in 89 (11.1%), and indeterminate in 11 (1.3%) patients. The median follow-up of patients with initial QFT-Plus test negative was 33.6 months (min–max: 3–76.3). Follow-up tests were carried out on only 59 (8.4%) of these 701 patients. Of the rescreened 59 patients, 56 had negative results, 3 had positive results. TB was developed in only 2 (0.25%) of the 801 patients during follow-up.

Conclusions: Assessment of LTBI in patients with SpA using interferon-gamma release assays (IGRAs) test is rational. Performance of annual testing of IGRAs in patients who were QFT negative was low in our SpA cohort. National and international guidelines may need to be updated to reflect real-world data and clinical practice.

Key words: tuberculosis; rescreening; spondyloarthritis; IGRA; biological/targeted DMARDs.

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Introduction

Biologic and targeted-synthetic disease modifying anti-rheumatic drugs (b/ts-DMARDs) are effective therapeutic agents for the treatment of inflammatory rheumatic diseases. On the other hand, b/ts-DMARDs such as tumor necrosis factor alpha inhibitors (TNFα-i) and Janus kinase inhibitors (JAK-i) may lead to increased susceptibility to infections and reactivation of latent infections such as tuberculosis (TB) [1,2]. The risk of reactivation TB has been reported to be 5–7 times higher in people receiving TNFα-i therapy than in the general population [3,4]. However, among 16,760 matched patients, the risk of TB in JAK-i users, although increased, was significantly lower than in b/ts-DMARDs users [2]. As a proinflammatory cytokine, TNFα-i is associated with the protection mechanism against the major *Mycobacterium* species [5]. Macrophage activation and granuloma formation disorders during anti-TNF therapy are well-known pathological mechanisms that predispose to mycobacterial infections [6]. Tofacitinib, used for the treatment of adult patients with rheumatoid arthritis (RA), is an approved small-molecule oral Janus kinase (JAK) inhibitor [7]. Tofacitinib primarily inhibits JAK3 and JAK1, regulating the immune response through downregulation of several cytokines (interleukins (ILs) 2, 4, 7, 9, 15, and 21) that are important for lymphocyte development and function [8]. Considering its mechanism of action, the risk of TB and other opportunistic infections may potentially be increased in patients treated with tofacitinib.

Therefore, national, and international health authorities recommend routine screening for latent TB infection (LTBI) before the initiation of TNFα-i

therapy; and when detected, providing prophylactic treatment [9,10]. However, the frequency of LTBI rescreening and monitoring in patients with inflammatory arthritis on biologic therapy remains unclear in clinical practice. Some national and international health authorities recommend annual LTBI screening for patients in whom LTBI was not detected initially. The incidence calculated according to the number of new and relapsed cases registered in TB control dispensaries was 13.5 per 100,000 in 2019, and 10.6 per 100,000 in 2021. The total case rate was 13.7 per 100,000 in 2019, and 10.7 per 100,000 in 2021 [11,12]. According to the World Health Organization (WHO) estimates, the TB incidence in Turkey was 16 per 100,000 in 2016. Turkey is in the medium-low incidence group in terms of TB incidence and registered case rate [13].

There is no universally accepted gold standard method for detecting LTBI. One of the most utilized screening tests is tuberculin skin test (TST), which has a significant limitation in that it can produce false positive results due to cross-reactivity with the Bacillus Calmette-Guerin (BCG) vaccine [14]. The QuantiFERON-TB Gold Plus (QFT-Plus; QIAGEN, Germantown, USA) test was developed to address this limitation and provide more specific screening [15]. We aimed to evaluate the impact of LTBI rescreening using the QFT-Plus test method, and to assess the frequency of rescreening in real-life spondyloarthritis (SpA) patients on b/ts-DMARDs.

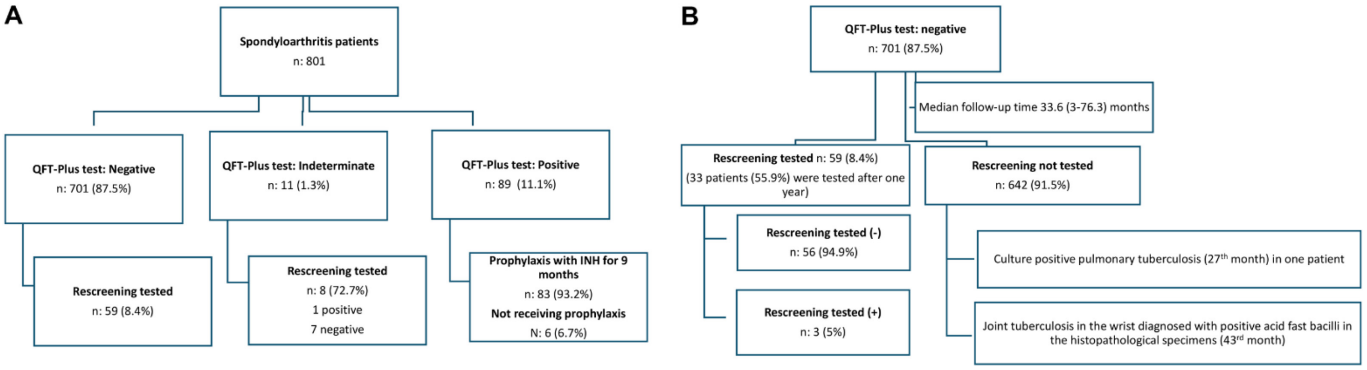
Methodology

Patients and study groups

The Hacettepe University Rheumatology Biologic Registry (HURBIO) database was established in 2005 and is a single-center database that registers and monitors patients with rheumatic diseases who are prescribed b/ts-DMARDs. It is also a database where detailed demographic characteristics, comorbidities, clinical and laboratory information, and the medications used are recorded. The database is used by physicians for following the patients who are being treated at the Rheumatology Department Clinic and Polyclinic, Department of Internal Medicine, Hacettepe University Faculty of Medicine. SpA patients who were using b/ts-DMARDs and whose detailed information was recorded in the HURBIO database were included in this study. This study focused on patients with a diagnosis of SpA who were scheduled for b/ts-DMARDs treatment and had undergone QFT-Plus testing for LTBI screening between October 2017 and December 2023. Demographic and clinical characteristics of SpA and LTBI were recorded retrospectively. Patients with less than 3 months follow-up after starting b/ts-DMARDs treatment until March 2024 were excluded from the study (Figure 1).

TST positivity in LTBI screening in communities where BCG vaccination is routinely applied, such as in our country, can be up to 61% [16]. This results in unnecessary TB prophylaxis. In order to prevent this situation, interferon-gamma release assays (IGRAs) have been preferred instead of TST in LTBI screening in our hospital since May 2011. QFT-Plus test results were analyzed by categorizing the data as positive, negative, or indeterminate. Patients with positive LTBI were given isoniazid (INH) for 9 months; and in cases where it could not be used, they were administered rifampin prophylaxis for 4 months [10]. b/ts DMARDs was started simultaneously with prophylaxis. When the QFT-Plus test negative patients underwent repeated QFT-Plus test during follow-up, the timing of these tests were also analyzed. The frequency of active TB disease, clinical features, and management of TB were recorded and assessed. The criteria for diagnosing active TB included symptoms related to the affected organ (cough lasting more than 3 weeks, sometimes

Figure 1A. QFT-Plus test follow-up of spondyloarthritis patients; **B.** Follow-up of spondyloarthritis patients with QFT-Plus test negative result.



bloody sputum, fever, night sweats, weight loss for lung TB; unexplained hematuria for renal TB; unexplained diarrhea for GIS TB; lymph node enlargement, etc.), at least one of the methods indicating TB infection (such as IGRA, purified protein derivative (PPD)) is positive, and there are findings compatible with TB in the affected organs with diagnostic methods (such as acid-fast bacillus (AFB), TB culture, imaging methods). After 2 months of initial treatment with INH, rifampicin, pyrazinamide, and ethambutol, patients with active TB were successfully treated with INH and rifampicin for a total of 9 months. No complications or hepatotoxicity developed. In cases where the result was indeterminate, repeat IGST or TST were recommended. In cases where the result was negative, a clinical decision was made for prophylaxis [10].

Our study was in accordance with the 2013 amendment of the Helsinki Declaration and ethical approval was obtained from the Hacettepe University Institutional Review Board (GO21/595, 04/05/2021).

QuantiFERON-TB Gold Plus test

The QFT-Plus test is an enzyme-linked immunosorbent assay (ELISA) based test that measures IFN-γ response from T cells stimulated by *Mycobacterium tuberculosis* antigen (ESAT-6 and CFP-10). The TB1 tube contains the ESAT-6 and CFP-10 peptide antigens that induce CD4 + T-cell response, while the TB2 tube contains additional shorter peptides of ESAT-6 and CFP-10 designed to stimulate both CD4 + and CD8 + T cells [17]. The QFT-Plus test was performed and evaluated according to the manufacturer's recommendations [18]. The QFT-Plus test results were recorded as positive, negative, or indeterminate.

The samples were collected directly into the QFT-Plus blood collection tubes (QIAGEN, Germantown, MD, USA), with 1 mL of blood added to each tube (Nil, TB1, TB2, and mitogen tubes). The tubes were shaken to mix the antigen with the blood and incubated at 37 ± 1°C as soon as possible, but no later than 16 hours after collection. After an overnight incubation period (16 to 24 hours), the tubes were centrifuged, the plasma was removed, and the amount of IFN-γ (IU/mL) was measured using an BioTek Epoch microplate reader (Agilent, Santa Clara, CA, United States). The microplate reader was used to measure optical density (OD) at 450 nm, with a reference filter set between 620–650 nm. After measuring the OD of the ELISA plate, the values were used to calculate the results. The QFT-Plus analysis software v2.71 was utilized for interpreting the results [19].

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, USA). Numerical variables conforming to normal distribution were investigated by visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk tests). Descriptive analyses of non-normally distributed numerical variables were expressed as median and inter-quartile range (IQR). The Chi-square or Fisher tests were used for analyzing categorical data and rates in independent groups. The Mann–Whitney U test was utilized to collate the median of non-normally distributed data of the independent groups. $p < 0.05$ was accepted as statistically significant.

Results

Demographic and clinical characteristics of patients

Out of the 946 SpA patients, those with a follow-up period of less than 3 months were excluded, and 801 patients (ankylosing spondylitis (AS)-nonradiographic axial spondyloarthritis (nrSpA)/psoriatic arthritis (PsA): 643 (80.3%)/158 (19.7%)) were included in the study. Of these 801 patients, 464 (57.9%) were female with a median age of 42.1 years (min–max: 19.3–78.6 years). The median follow-up time after initiation of b/ts-DMARDs treatment was 33.9 months (min–max: 3–76.4 months). The distribution of first biologic agents were TNFα-i in 773 (96.5%) patients, and IL-17 and IL-23 inhibitors in 28 (3.5%) patients. Distribution of b/ts-DMARDs agents used during follow-up were TNFα-i in 779 (97.3%) patients, JAK-i in 35 (4.4%) patients, and IL-17 and IL-23 inhibitors in 159 (19.9%) patients. There was no difference between QFT-Plus negative and positive patients regarding the initial and follow-up b/ts-DMARDs treatment choices.

Comparison of patients with SpA based on QFT-Plus test results

Out of the 801 patients with SpA, 89 (11.1%) had a positive QFT-Plus test result, while 701 (87.5%) tested negative, and 11 (1.3%) had indeterminate results. Those with a positive QFT-Plus test result were notably older compared to the patients with negative results ($p < 0.001$). Gender, smoking history, and laboratory results were comparable between the two groups ($p > 0.05$). When assessing comorbidities, it became evident that the QFT-Plus test positive group had a higher frequency of chronic obstructive pulmonary disease and hypertension (Table 1).

Distribution of patients according to IGRAs test and follow-up for LTBI

A total of 89 patients with positive QFT-Plus tests were followed for a median 42.9 months (min–max: 3.2–73 months). INH prophylaxis was administered for a duration of 9 months to 83 (93.2%) of the 89 patients. The remaining 6 patients (6.7%) did not receive INH prophylaxis due to non-compliance. No case of TB was observed in any of 89 patients during the follow-up period.

Eight of the 11 patients with indeterminate test results underwent follow-up QFT-Plus test. The median time interval between the two tests was 25.6 days (min–max: 4–98 days). One patient's retest was positive, while the remaining 7 patients' retests were negative. The median disease follow-up period of the 701 patients who tested negative with QFT-Plus test after the initiation of biologic treatment was 33.6 months (min–max: 3–76.3 months). Of the patients with negative QFT-Plus tests at baseline, 539 (76.9%) were followed for a period exceeding 12 months following the initiation of biologic therapy. Follow-up QFT-Plus tests were carried out in only 59 (8.4%) of the 701 patients who initially tested negative with the QFT-Plus test, during routine follow-up at the discretion of the monitoring physician, regardless of symptoms. Among them, 56 patients had negative results, while 3 patients had positive results. The median time interval between the two QFT-Plus tests was 12.3 months (min–max: 3.1–43 months). Of the 59 patients who underwent follow-up QFT-Plus test, 26 (44.1%) had the follow-up test within the first year and 33 (55.9%) after 1 year. The patients with a positive follow-up QFT-Plus test, were tested after 4 months (1 patient), 28 months (1 patient), and 31 months (1 patient). Notably 3 patients had no active TB and were subsequently followed-up with INH prophylaxis for a period of 9 months.

Only 2 (0.25%) patients who were QFT-Plus test negative at the beginning of biologic therapy developed TB during follow-up. Primary TB was not excluded. The first patient was a 46-years-old male who did not have a follow-up test. He was admitted with symptoms of cough, yellow sputum, rapid weight loss (7–8 kg in 1 month), and night sweats; and diagnosed with culture positive pulmonary TB on the 27th month of biological therapy (adalimumab). The other patient was a 51-years-old female who had complaints of swelling, pain, and redness on the dorsum of her right hand. She was diagnosed with joint TB in the right wrist, with the demonstration of positive AFB in the histopathological specimens in the 43rd month of etanercept therapy. QFT-Plus test positivity developed at the same time.

Discussion

In this study, only 8.4% of patients with SpA were rescreened for LTBI during follow-up after a median of 33.6 months. Three asymptomatic patients were positive during rescreening tests, and INH prophylaxis was added while they continued their biologic treatment. Remarkably, only 2 (0.25%) of the patients who were QFT-Plus test negative at the beginning of biologic therapy developed TB during follow-up.

Table 1. Comparison of patients with SpA, grouped by QFT-Plus test results.

	QFT-Plus Test		*p* value
	Positive (n = 89)	Negative (n = 701)	
Female, n (%)	46 (51.7)	411 (58.6)	0.21
AS-nrSpA	67 (75.3)	568 (81)	0.19
PsA	22 (24.7)	133 (19)	
Age, years, median (min–max)	53.1 (24–76.3)	41.1 (19.3–78.6)	< 0.001
Comorbidities, n (%)			
Diabetes mellitus	6 (6.7)	55 (7.8)	0.71
Hypertension	18 (20.2)	84 (12)	0.02
Chronic renal failure	0 (0)	2 (0.3)	1
Chronic obstructive pulmonary disease	4 (4.5)	9 (1.3)	0.04
Coronary artery disease	4 (4.5)	14 (2)	0.13
Smoking, n (%)			
Never	30 (33.7)	293 (41.8)	0.14
Ever	59 (66.3)	408 (58.2)	
Laboratory tests, median (min–max)			
Leukocyte, $*10^3$/mL	7.8 (4.1–16.8)	7.7 (2.4–81)	0.64
Neutrophil, $*10^3$/mL	4.7 (0.8–7.9)	4.6 (0.7–16.5)	0.68
Lymphocyte, $*10^3$/mL	2.1 (0.8–7.2)	2.1 (0.3–5.8)	0.93
Thrombocyte, $*10^3$/mL	270 (146–585)	282 (24–573)	0.33
Hemoglobin, g/dL	13.5(10.3–16.9)	13.5 (8.4–18.1)	0.58
ESR, mm/h	19 (2–120)	19 (2–113)	0.69
CRP, mg/dL	0.8 (0.1–17.1)	0.8 (0.1–46.4)	0.89
QFT-Plus Indeterminate results: 11 (1.3%) patients			

SpA: spondyloarthritis; AS-nrSpA: ankylosing spondylitis-nonradiographic axial spondyloarthritis; PsA: psoriatic arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

In line with the recommendations of the Assessment of Spondylarthritis International Society (ASAS)-EULAR 2022 axial spondyloarthritis and 2019 Psoriatic Arthritis Treatment Guidelines, biological treatments are recommended for non-steroidal anti-inflammatory drugs (NSAID) unresponsiveness. Accordingly, biological treatments are frequently used for the SpA group of diseases by clinicians [20,21]. It is important to note that national and international health authorities recommend routine screening for LTBI before the initiation of TNFα-i, along with prophylactic treatment, if LTBI is detected. Numerous guidelines for LTBI screening prior to the use of biologic agents have been issued by various countries and international organizations [18,22]. These recommendations emphasize the importance of obtaining a comprehensive patient history, identifying TB risk factors, conducting a chest radiograph, and promptly diagnosing and treating suspected active TB. These principles represent a consensus within the medical community [23].

There is still no consensus on the use of TSTs and/or IGRAs for LTBI screening before initiating biologic agents. There are various approaches in the guidelines, such as using TST only, IGRAs only, using a combination of TST and IGRAs, and applying TST initially followed by IGRAs according to the results [18]. Additionally, there is a lack of consensus on whether and when to repeat these tests during patient follow-up. While most countries do not provide specific recommendations in this regard, some countries, such as Turkey, advise annual rescreening [24]. There are no robust data to define how often rescreening should be performed and/or if there is a need to rescreen patients who switch b/ts-DMARDs; it is a subject that needs to be investigated. Given the regional differences in TB-burden and also issues (e.g., cost) that might affect the availability of some new tests like QFT-Plus, national and international guidelines should also be followed, where available [25].

The 2016 guidelines issued by the national health authority in Turkey suggests that either IGRAs or TST can be used before the initiation of TNFα-i [10]. We screened the patients with TST prior to the initiation of biologic agents from 2005 to 2011, with the QuantiFERON TB Gold-in Tube (QFT-GIT) test since May 2011, and the QFT-Plus test since May 2017. The presence of active TB is a contraindication for commencing TNFα-i therapy; hence, active TB must be ruled out beforehand. The national guideline also recommends that TB screening for patients receiving TNFα-i should be repeated every 6 months, and LTBI screening should be repeated annually. Even when patients starting TNFα-i are asymptomatic, clinical evaluations for TB should be conducted every 3 months, and radiological assessments should be performed every 6 months. However, symptomatic patients should be monitored for TB by the relevant specialist, regardless of the duration of symptoms [10]. In our study, only 8.4% of patients who had negative QFT-Plus test at the initiation of b/ts-DMARDs treatment, underwent annual LTBI screening. Patients refer to our clinic for follow-up visits every 3–6 months following the initiation of b/ts-DMARDs treatment, during which physicians assess them for TB symptoms and potential side effects of the treatment.

Most studies related to the screening of LTBI in patients considered for TNFα-i therapy, have included mixed rheumatic disease groups and evaluated the TB risk without a clear distinction between different diseases within the group. The failure to differentiate these diseases has raised concerns about the reliability due to the varying groups of drugs used in different diseases and the varying potential for immunosuppression of different diseases. There are very few studies in the literature that focus solely on patients with SpA. It is well-established that the initial 6–12 months following the initiation of a biologic agent represents the highest risk period for the development of active TB [26,27]. However, there are also studies in the literature showing that TB develops over a longer period of follow-up. It was determined that 12 (5.5%) of 218 SpA patients included in a study conducted in Brazil developed active TB during an average follow-up period of 5.8 years. TB infection developed in 8 of these patients (66.6%) an average of 22.8 months after starting TNFα-i use, and it was observed that the majority of them were in the form of pulmonary TB. Extrapulmonary TB occurs in 75% of patients who develop TB within the first year of starting TNFα-i, and in 25% of patients who develop TB more than a year after starting TNFα-i [28]. Immunocompromised patients are at higher risk for developing TB in countries with high TB prevalence. Therefore, we suggest that patients who are starting biologic therapy in these countries should be rescreened at baseline and annually. Our study was conducted in Turkey which has low-medium tuberculosis burden. Consistent with the literature, 2 patients developed active TB after more than 1 year of starting treatment. There was 1 case with pulmonary TB and 1 case with extrapulmonary TB. Both patients had negative initial IGRAs and did not undergo follow-up IGRAs.

Our study stands out in the literature as currently there are no studies that have evaluated patients diagnosed with SpA and starting biologic treatment with follow-up QFT-Plus test. The inclusion of a homogeneous patient group consisting solely of SpA diagnosis; the substantial number of patients involved; and the meticulous follow-up of these patients, both in terms of follow-up QFT-Plus test and TB infection; represent the strengths of our study, that we believe can make valuable contributions to both the scientific literature and real-world clinical practice. In a study from Korea, IGRAs transformation was detected in 10 (7.9%) of 127 ankylosing spondylitis patients with a median TNFα-i follow-up period of 21.5 months [29]. According to this study, the reason for this high rate is that Korea is a moderate TB burden region and poses a greater risk of exposure to TB [30]. However, the number of patients in this study was significantly less than ours and the IGRAs test used was the QFT-GIT test. Furthermore, our study is distinct in its use of the QFT-Plus test as an IGRAs method. QFT-Plus test is a new generation of IGRAs which includes an additional TB2 tube that enables the stimulation of both CD4+ and CD8+ T cells to produce IFN-γ. Thus, the QFT-Plus test seems to have an advantage over QFT-GIT test in the high risk-population of immunosuppressed patients, as was the setting in our study. A recent meta-analysis revealed that both tests performed similarly in the immunosuppressed population, with QFT-Plus showing a slightly higher sensitivity than QFT-GIT in detecting positive cases [31]. Although the current study was not conducted to compare the QFT-Plus and QFT-GIT tests in terms of LTBI detection, we think that the presence of two TB antigen tubes, may have an advantage in detecting positive patients in high-risk groups. Since the current study focused only on SpA, an almost homogenous population of a disease group, the possible bias noted in Zhang *et al*.'s meta-analysis [31], was overcome in our study.

The use of a reliable test for the detection of LTBI helps to avoid the administration of unnecessary INH prophylaxis which increases patient cost and potential hepatotoxicity. In a multicenter study, it was shown that the number of patients who would receive this treatment could be decreased by half when IGRAs were used instead of TST in the screening of latent TB before biologic treatment [32]. Nevertheless, it is worth noting that the availability of the QFT-Plus test may vary and could potentially impose a financial burden on the patients.

The main limitations of our study include its retrospective design, and the low number of rescreening tests in our patients.

Conclusions

This study showed that assessment of LTBI in patients with SpA using IGRAs worked well. It is crucial to continuously monitor patients on biologic agents for symptoms indicative of active TB during their follow-up. Performance of annual testing of IGRAs in patients with QFT-Plus negative was low in our SpA cohort. On the other hand, the occurrence of TB infection or conversion of QFT-Plus test negative patients over a median follow-up period of 33.6 months was exceedingly rare (only 2 patients). The findings suggest that annual rescreening may not be necessary for all QFT-Plus negative patients, particularly in low-moderate TB burden settings, considering the hepatotoxicity of INH given for possible LTBI and the financial burden of using QFT-Plus. These results suggest that there may be a need to update the national and international guidelines in line with real-world data and clinical practice.

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Authors' contributions

The study was designed by all the coauthors. Analysis was performed by OK, ZO, LK, EB, AÖ and AE. Manuscript preparation and approval involved all the coauthors. LK and OK are the guarantors.

Ethics approval

The Hacettepe University Institutional Review Board provided ethical approval for this study (GO21/595, 04/05/2021).

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Conflict of interests

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