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Assessing latent tuberculosis infection prior to biologic therapy in psoriasis: a new diagnostic approach with an online interpreter

Psoriasis'te biyolojik tedavi öncesi latent tüberküloz enfeksiyonunun değerlendirilmesi: web tabanlı yorumlayıcı ile yeni bir tanı yaklaşımı

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Abstract

Purpose: The use of biological agents, particularly anti-TNF-alpha treatments, is associated with an elevated risk of tuberculosis (TB). Hence, a comprehensive assessment of latent tuberculosis infection (LTBI) before biologic therapies is imperative. The objective of this study was to evaluate the utility of an online tuberculin skin test (TST)/ interferon-γ release assay (IGRA) interpreter (OI-TST/IGRA) in assessing the risk of LTBI prior to initiating biological therapies in psoriasis patients.

Materials and methods: 116 psoriasis patients who were previously evaluated for TB by a pulmonologist before being treated with a biologic agent were re-evaluated retrospectively with OI-TST/IGRA (tstin3d.com). Mean positive predictive value (PPV), mean annual risk of development of active tuberculosis (ARDATB), and mean cumulative risk of active tuberculosis (CRATB) values were calculated with OI-TST/IGRA and compared with previous results. Group comparisons were performed using Kruskal-Wallis and Mann-Whitney U tests.

Results: The PPV of the LTBI-positive group was significantly higher than the LTBI-negative group. The PPV and ARDATB values of the TST size of >15 mm group were significantly higher than the TST size of 5-9 mm and TST size of 10-15 mm groups. The PPV, ARDATB, and CRATB values of the QuantiFERON-TB Gold In-tube test (QFT-GIT)-positive group were significantly higher than the QFT-GIT-negative group. And the same values of the chest X-ray (CXR)-positive group were significantly higher than the CXR-negative group. The PPV, ARDATB, and CRATB values were positively correlated with TST, QFT-GIT and CXR results. In addition, the PPV was positively correlated with previous LTBI decisions.

Conclusion: OI-TST/IGRA in which many factors are questioned and PPV, ARDATB, and CRATB values are evaluated together, may be a valuable tool for assessing the risk of active TB in psoriasis patients and preventing overdiagnosis and unnecessary prophylaxis.

Keywords: Latent tuberculosis infection, psoriasis, biologic therapy.

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Öz

Amaç: Biyolojik ajanların, özellikle de anti-TNF-alfa tedavilerinin kullanımı artmış tüberküloz (TB) riski ile ilişkilidir. Bu nedenle, biyolojik tedavilerden önce latent tüberküloz enfeksiyonunun (LTBI) kapsamlı bir şekilde değerlendirilmesi gereklidir. Bu çalışmanın amacı, psöriazis hastalarında biyolojik tedavilere başlamadan önce LTBI riskini değerlendirmek için web tabanlı bir uygulama olan tüberkülin deri testi (TST) /interferon-γ salınım testi (IGRA) (OI-TST/IGRA) yorumlayıcısının faydasını değerlendirmektir.

Gereç ve yöntem: Biyolojik bir ajanla tedavi edilmeden önce göğüs hastalıkları uzmanı tarafından TB açısından değerlendirilen 116 psoriasis hastası retrospektif olarak OI-TST/IGRA (tstin3d.com) ile yeniden değerlendirildi. OI-TST/IGRA ile ortalama pozitif prediktif değer (PPV), ortalama yıllık aktif tüberküloz gelişme riski (ARDATB) ve ortalama kümülatif aktif tüberküloz riski (CRATB) değerleri hesaplandı ve önceki sonuçlarla karşılaştırıldı. Grup karşılaştırmaları Kruskal-Wallis ve Mann- Whitney U testleri kullanılarak yapılmıştır.

Bulgular: LTBI-pozitif grubun PPV'si, LTBI-negatif gruptan anlamlı olarak daha yüksekti. TST boyutu >15 mm olan grubun PPV ve ARDATB değerleri, TST boyutu 5-9 mm ve TST boyutu 10-15 mm olan gruplardan anlamlı olarak daha yüksekti. QuantiFERON-TB Gold In-tube test (QFT-GIT) pozitif grubun PPV, ARDATB ve CRATB değerleri QFT-GIT negatif gruptan anlamlı derecede yüksekti. Akciğer grafisi (CXR) pozitif grubun aynı değerleri CXR negatif gruptan anlamlı derecede yüksekti.

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PPV, ARDATB ve CRATB değerleri TST, QFT-GIT ve CXR sonuçları ile pozitif korelasyon göstermiştir. Ayrıca, PPV önceki LTBI kararları ile pozitif korelasyon göstermiştir.
Sonuç: Birçok faktörün sorgulandığı ve PPV, ARDATB ve CRATB değerlerinin birlikte değerlendirildiği OI-TST/IGRA, psoriasis hastalarında TB riskinin değerlendirilmesinde, yanlış tanı ve gereksiz profilaksinin önlenmesinde değerli bir araç olabilir.

Anahtar kelimeler: Latent tüberküloz enfeksiyonu, psöriazis, biyolojik tedavi.

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Introduction

Psoriasis is an inflammatory and chronic disease with about 3% of prevalence worldwide. It may be associated with significant comorbidities, such as psoriatic arthritis, uveitis, metabolic syndrome, psychiatric and cardiovascular diseases that poorly affect patients' quality of life [1-3].

The use of biologics targeting tumor necrosis factor-α (TNF-α), the primary cytokine in the development of psoriasis, has proven to be highly effective in the treatment of the disease. With the increasing use of anti-TNF-α biologics, a new group of high-risk patients for tuberculosis (TB) has developed. This has led to the need for increased awareness and effort to screen latent tuberculosis infection (LTBI) with clinical, radiographic, and laboratory measures [4, 5].

Before the treatment with anti-TNF-α biologics, detailed personal and familiar anamnesis about TB, including BCG vaccination, household contact with a TB case, immigration from or journey to a nation with a high incidence of TB, occupation (healthcare workers, etc.), smoking, alcohol consumption, and diabetes mellitus should be evaluated with great attention. On the other hand, chest X-ray (CXR), computed tomography (CT) of thorax, tuberculin skin test (TST), and interferon-γ release assays (IGRAs) like QuantiFERON-TB Gold In-tube test (QFT-GIT) are widely used to determine the TB risk more objectively [6]. For more than a century, TST has been employed as a standard method for screening TB. However, some TST limitations, such as koebnerization phenomena and false positivity associated with previous BCG or contacting with non-tuberculous mycobacteria, maybe the reasons that resulted in the growing acceptance and popularity of the IGRAs in clinical practice in the last decade [7-9]. A gold standard test is still not available for establishing LTBI. The difficulty in inventing a novel test is related neither to sensitivity nor specificity but to the predictive value [10].

The 'Online TST/IGRA Interpreter' (OI-TST/IGRA) (tstin3d.com) is suggested to be a useful clinical tool for screening LTBI in adult patients. This calculator aims to approximate the risk of active TB in a patient with a TST size of ≥ 5 mm, based on his/her related medical outcomes and specific conditions [8, 11, 12]. The calculation needs the information about current and immigration age (for individuals who migrated to a country with a low incidence of TB), size of TST, IGRA, BCG status, place of birth, and recent contact with an active TB patient. Besides, a total of 15 parameters are asked, such as anti-TNF-α therapy, diabetes mellitus, abnormal CXR findings, chronic renal failure, etc. (Table 1).

OI-TST/IGRA calculates the positive predictive value (PPV) of the test, the annual risk of development of active TB (ARDATB), the cumulative risk of active TB (CRATB) up to age 80, and the probability of drug-induced hepatitis and related hospitalization if the patient treated with isoniazid. Table 2 presents the OI-TST/IGRA results of a sample patient.

In this study, it was aimed to use the OI-TST/IGRA to re-assess the previously established diagnosis of LTBI before the biologic therapies in psoriasis by conventional procedures that are thus far mainly based on TST and/or IGRA and clinical profile. Based on literature reviews, this study is the first, investigating the usability of OI-TST/IGRA to determine active TB risk in patients with psoriasis. Considering the challenges of LTBI investigation and overestimation risk of LTBI diagnosis, OI-TST/IGRA may provide a new and hopeful perspective on this issue.

Table 1. Parameters of the online TST/IGRA interpreter

Age				
Age at immigration (If person immigrated to a low TB incidence country)				
Country of birth				
TST size (TST<5 mm is not included in the calculator)	Not done	5-9 mm	10-15 mm	15> mm
IGRA result	Not done	Negative	Positive	
BCG vaccination	Never vaccinated or unknown	Vaccinated age<2 years	Vaccinated age≥2 years	
Recent contact with active tuberculosis	No contact	Close contact	Casual contact	
Other conditions				
· AIDS				
· Abnormal chest x-ray: granuloma				
· Abnormal chest x-ray: fibronodular disease				
· Carcinoma of head and neck				
· Chronic renal failure requiring hemodialysis				
· Cigarette smoker (>1 pack/day)				
· Diabetes mellitus (all types)				
· HIV infection				
· Recent tuberculosis infection (tuberculin skin test conversion≤ 2 years ago)				
· Transplantation (requiring immune-suppressant therapy)				
· Silicosis				
· Treatment with glucocorticoids				
· TNF-α inhibitors (e.g., infliximab/etanercept)				
· Underweight (<90% of ideal body weight or a body mass index≤ 20)				
· Young age when infected (0-4 years)				

TB tuberculosis, *TST* tuberculin skin test, *IGRA* interferon-γ release assay

Table 2. Online TST/IGRA Interpreter results of a sample patient

Patient Data
1. TST size of>15 mm
2. Positive IGRA test
3. 68 years old, born in Türkiye
4. BCG status; vaccinated age<2 years
5. No contact with active tuberculosis
6. Abnormal chest X-ray: fibronodular disease
7. TNF-α inhibitors (e.g., infliximab/etanercept)
Results
1. The likelihood that this is a true positive test (PPV) is: 99.71%
2. The ARDATB is estimated to be 1.78%
3. The CRATB, up to the age of 80, is: 21.36%
4. If treated with INH the probability of drug-induced hepatitis is 5% and the probability of hospitalization for drug-induced hepatitis is 2.4%

TST tuberculin skin test, *IGRA* interferon-γ release assay, *PPV* positive predictive value, *ARDATB* annual risk of development of active TB *CRATB* cumulative risk of active TB, *INH* isoniazid

Materials and methods

Subjects

One hundred-sixteen psoriasis patients treated with a biologic agent between October 2016 and March 2019 in Kayseri City Education and Research Hospital (Department of Dermatology and Venereology) were reviewed using a software called PSORTAKSIS. The software has been in use for psoriatic patients since 2016 [13]. It includes patients' data such as demographics, overall personal and familial medical history, accompanying diseases, laboratory results, previous and current treatments, etc. Records of the local tuberculosis dispensary (Melikgazi Tuberculosis Dispensary, Kayseri, Turkey) were also evaluated. The study approved by Ethics Committee of Kayseri City Education and Research Hospital.

Conventional searching procedures for LTBI

Screening LTBI was performed routinely before all biologic therapies for psoriasis according to the Turkish Psoriasis Biologic Agent Usage Guideline (2010) [14]. Diagnosis of LTBI, the decision for prophylactic anti-tuberculosis treatment, the initiation time of biologics (simultaneously or one month later, etc.), and follow-up were all performed by a pulmonologist.

All TSTs were performed at a local tuberculosis dispensary, and the QFT-GIT tests were performed at a private laboratory. TSTs were conducted conventionally by injecting five tuberculin units. The measurement of skin induration was documented 48-72 hours after injection. The cutoff for considering a result positive was determined as ≥ 10 mm for the patients; all were BCG-vaccinated. QFT-GIT tests were administered following the guidelines provided by the manufacturer. Interferon-γ value of 0.35 IU/mL or greater was defined as a positive result. In all patients, TST was repeated every three months and QFT-GIT test annually [14]. Furthermore, after the initial assessment, CXR was repeated every six months. A CT scan was obtained in patients with suspicious CXR findings.

Re-assessment of predetermined LTBI with OI-TST/IGRA

Patients previously diagnosed with LTBI by a pulmonologist underwent a re-assessment using OI-TST/IGRA, targeting those with a TST size of ≥5 mm. Forty-three patients had a <5 mm TST size and were eliminated to re-assess. Therefore, calculations were made individually for seventy-three patients. PPV, ARDATB, and CRATB values were calculated with OI-TST/IGRA version 3.0 [11]. Test results were analyzed according to the groups based on previous LTBI decisions, TST sizes, QFT-GIT results, and CXR findings.

Statistical analysis

Utilizing the "Statistical Package for the Social Sciences (SPSS ver. 21.0 for Windows, IBM Corp., Armonk, NY, USA)", we conducted analysis on the data. A level of significance was assigned to p-values, with $p<0.05$ deemed significant. Using the Shapiro-Wilk and Kolmogorov-Smirnov tests, the normality assumption for quantitative variables was assessed. The group comparisons of continuous variables in the study were carried out using the Kruskal-Wallis test, considering the fulfillment of assumptions. Following the Kruskal-Wallis test, pairwise comparisons of groups showing significant differences were executed using the Mann-Whitney U test, and the results were evaluated with Bonferroni correction (0.05/group number). The agreement between TST/IGRA (tstin3d.com) PPV value classes and LTBI, TST, QFTGT and CXR test decisions were examined using Kappa values.

Relationships between categorical variables were examined by taking into account the variable type and the number of categories of categorical variables. Relationships between continuous variables were examined with Spearman correlation analysis. Relationships between categorical variables were examined by taking into account Phi (φ) coefficient, Cramer's V correlation coefficients and Fisher Exact test results. The relationships between dichotomous nominal variables and continuous variables were examined with Point Biserial Correlation coefficients.

Results

Of the 116 patients, there was no medical history of HIV infection or immunosuppressive therapy. The country of birth was the Republic of Türkiye in all patients with no history of immigration. They were all vaccinated with BCG before two years of age and did not give a history of recent contact with an active TB patient.

Among the individuals excluded from the study due to a TST size of <5 mm (n=43), 13 received anti-TNF-α biologic treatment, while 30 underwent treatment with an interleukin (IL) antagonist. LTBI diagnoses were made in 10 of these patients; however, TST and QFT-GIT were negative for all. CXR had suspicious findings in two of them. Three patients with LTBI received anti-TNF-α biologic, and seven received IL antagonist.

Among the participants included in the study (TST size of ≥5 mm, n=73), the average age (±SD) was 45.50±11.46 years. 26 of them received anti-TNF-α biologic, which is accepted as one of the risk conditions in OI-TST/IGRA, and 47 were treated with an IL antagonist, which was not included as a risk factor. Additionally, 4 patients had diabetes mellitus which is also accepted as a risk factor in OI-TST/IGRA. The patients did not have any other conditions that could potentially increase the risk of tuberculosis.

Table 3 summarizes the statistical analysis of OI-TST/IGRA results according to the groups based on previous LTBI decisions, TST sizes, QFT-GIT results, and CXR findings. Of the patients, 89% (n=65) were grouped as LTBI-positive and 11% as LTBI-negative (n=8). The mean PPV value of the LTBI-positive group was significantly higher than the LTBI-negative group (p<0.05). Both ARDATB and CRATB values of the LTBI-positive group were higher than LTBI negative group, but this difference was not statistically significant (p>0.05).

When OI-TST/IGRA results were evaluated in terms of TST size (TST-a group: 5-9 mm, TST-b group: 10-15 mm, and TST-c group: >15 mm), the differences between TST size groups in terms of PPV and ARDATB values were found to be statistically significant (p<0.01, p<0.05, respectively). The difference between TST size groups in terms of CRATB values was not statistically significant (p>0.05). The difference between TST-a and TST-b groups in terms of mean PPV and ARDATB values was not statistically significant (p>0.05). However, mean PPV and ARDATB values of the TST-c group were significantly higher than the other groups (p<0.01, p<0.05, respectively). The mean PPV, ARDATB, and CRATB values of the QFT-GIT-positive group were significantly higher than the QFT-GIT-negative group (p<0.01). Furthermore, mean PPV, ARDATB and CRATB values of CXR-positive group were significantly higher than CXR-negative group (p<0.05, p<0.01, and p<0.01, respectively).

Correlations between LTBI decision, TST, QFT-GIT, CXR, mean PPV, ARDATB, and CRATB values are presented in Table 4. According to these coefficients, positive correlations were found between LTBI decision and mean PPV value (r=0.269, p<0.05), TST and CXR (r=0.293, p<0.05), TST and mean PPV value (r=0.310, p<0.01), TST and mean ARDATB value (r=0.323, p<0.01), TST and mean CRATB value (r=0.308, p<0.01), QFT-GIT result and mean PPV value (r=0.896, p<0.01), QFT-GIT result and mean ARDATB value (r=0.400, p<0.01), and QFT-GIT result and mean CRATB value (r=0.314, p<0.01). A positive correlation was also found between CXR and mean PPV value (r=0.272, p<0.05), CXR and mean ARDATB value (r=0.736, p<0.01), and CXR and mean CRATB value (r=0.720, p<0.01).

Patients were categorized into three groups based on their PPV as low (<10%), intermediate (10-50%), and high (50-100%) [12]. None of the patients participating in the study were in the low PPV group. There were three patients (4.1%) in the intermediate and 70 patients (95.9%) in the high group. Inter-rater reliability is determined by assessing the agreement between scores provided by two or more raters, representing the degree of consistency among evaluators [15]. The Kappa statistic, introduced by Cohen, is commonly utilized for evaluating inter-rater reliability [16]. This statistical measure gauges the extent to how observer agreement deviates from chance agreement, especially in contexts involving categorical or nominal scales. The Kappa value typically falls within the range of -1 to 1. Positive values indicate that the agreement between observers is greater than would be expected by chance, while negative values suggest that chance agreement is more prevalent. A value of 0 indicates that the

agreement between observers is at the level expected by chance. The close-to-0 Kappa coefficients in Table 5 indicate either a lack of genuine agreement among evaluators or agreement occurring at a random level. The relationship between PPV groups and LTBI decision, TST result, QFT-GIT result, and CXR finding was not statistically significant (p>0.05). When the Kappa values were examined, it was found that there was no significant agreement (p>0.05) (Table 5).

Table 3. Analysis of Online TST/IGRA Interpreter results according to the groups based on LTBI decision, TST size, QFT-GIT result, and CXR finding

		n (%)	PPV, median (minimum-maximum)	ARDATB, median (minimum-maximum)	CRATB, median (minimum-maximum)
LTBI decision	Negative	8 (11.0)	60.06 (44.75-80.10)	0.075 (0.05-0.32)	2.83 (1.79-14.12)
	Positive	65 (89.0)	69.07 (45.87-99.70)	0.30 (0.05-1.78)	8.96 (0.65-62.01)
	$p^{\&}$		0.018	0.095	0.497
TST size	TST-a group (5-9 mm)	38 (52.1)	63.18 (44.75-99.39)	0.17 (0.05-1.77)	6.16 (0.65-62.01)
	TST-b group (10-15 mm)	22 (30.1)	65.86 (49.40-99.45)	0.07 (0.05-1.24)	3.07 (1.43-42.89)
	TST-c group (> 15 mm)	13 (17.8)	84.62 (71.20-99.70)	0.89 (0.08-1.78)	22.76 (1.44-54.74)
	p^{*}		0.000	0.024	0.095
	p^{a-b}		0.311	0.975	
	p^{a-c}		0.000	0.014	
	p^{b-c}		0.000	0.010	
QFT-GIT result	Negative	53 (72.6)	64.56 (44.75-84.99)	0.24 (0.05-1.52)	7.65 (0.65-47.17)
	Positive	20 (27.4)	99.34 (99.25-99.70)	0.53 (0.10-1.78)	19.27 (2.48-62.01)
	$p^{\&}$		0.000	0.000	0.007
CXR finding	No suspect finding for tuberculosis	54 (74.0)	64.99 (44.75-99.70)	0.08 (0.05-0.81)	2.87 (0.65-17.51)
	Suspect findings for tuberculosis	19 (26.0)	70.30 (50.81-99.66)	0.92 (0.06-1.78)	32.20 (0.92-62.01)
	$p^{\&}$		0.018	0.000	0.000

p^{*}: Kruskal- Wallis, p^{a-b}, p^{a-c}, p^{b-c}, $p^{\&}$: Mann-Whitney U, PPV positive predictive value, *ARDATB* annual risk of development of active tuberculosis *CRATB* cumulative risk of active tuberculosis disease, *LTBI* latent tuberculosis infection, *TST* tuberculin skin test, *QFT-GIT* QuantiFERON-TB Gold In-tube test, *CXR* chest X-ray

Table 4. Correlation coefficients between the variables

Parameters	LTBI	TST	QFT-GIT	CXR	PPV	ARDATB	CRATB
LTBI decision	1	0.074	0.216	0.108	0.269*[a]	0.191	0.146
TST		1	0.121	0.293*[a]	0.310**[b]	0.323**[b]	0.308**[b]
QFT-GIT			1	0.196	0.896**[b]	0.400**[b]	0.314**[b]
CXR				1	0.272*[a]	0.736**[b]	0.720**[b]
PPV					1	0.531**[b]	0.130
ARDATB						1	0.801**[b]
CRATB							1

LTBI latent tuberculosis infection, *TST* tuberculin skin test, *QFT-GIT* QuantiFERON-TB Gold In-tube test, *CXR* chest X-ray
PPV positive predictive value, *ARDATB* annual risk of development of active tuberculosis, *CRATB* cumulative risk of active tuberculosis
[a] Weak positive correlation, [b] Strong positive correlation, *:<.05, **:<01

Table 5. The relationship between PPV groups and LTBI decision, TST result, QFT-GIT result, and CXR finding

		PPV				
		Intermediate (10-50%) (n=3) n (%)	**High (50-100%) (n=70) n (%)**	***P* (Fisher exact)**	**Kappa value**	***P* (Kappa)**
LTBI decision	**Negative**	1 (12.5)	7 (87.5)	0.298	0.130	0.205
	Positive	2 (3.1)	63 (96.9)			
TST result	**Negative**	3 (5.0)	57 (95.0)	0.550	0.018	0.410
	Positive	0 (0.0)	13 (100)			
QFT-GIT result	**Negative**	3 (5.7)	50 (94.3)	0.557	0.032	0.277
	Positive	0 (0.0)	20 (100.0)			
CXR finding	**Negative**	3 (5.6)	51 (94.4)	0.563	0.030	0.294
	Positive	0 (0.0)	19 (100.0)			

PPV positive predictive value, *LTBI* latent tuberculosis infection, *TST* tuberculin skin test, *QFT-GIT* QuantiFERON-TB Gold In-tube test
CXR chest X-ray

Discussion

In the diagnosis of LTBI and the recommendation of TB prophylaxis, accurately determining an individual's risk ratio for developing active TB is a crucial step. Proper identification of cases with LTBI before the anti-TNF-α treatment is a prerequisite to avoid possible over-treatment with anti-tuberculosis agents and to identify patients who would benefit from anti-tuberculosis treatment accurately. If proper identification is not performed, unnecessary cost, time-consuming, increased risk of anti-tuberculosis drug resistance, and adverse side effects may be inevitable [17]. Unfortunately, a widely accepted guideline or consensus is not existing in this issue [12]. Lee et al. [18] stated that evaluating patients on biologics for LTBI is critical to reducing the risk of active TB. They proposed clinicians consider the insufficiency of actual methods and use all available facilities, including risk factor assessment, to estimate risk extensively.

Although many current guidelines encourage LTBI screening before all biologics, OI-TST/IGRA does not regard IL antagonists as risk factors for progressing to active TB [14, 19, 20]. In a cohort study including 12.319 patients with psoriasis, psoriatic arthritis, or ankylosing spondylitis, it was found that LTBI was reported as an uncommon adverse event after secukinumab therapy. This finding contradicts earlier research that indicated secukinumab was not linked to a heightened risk of tuberculosis [21]. Cho et al. [22] reported that ustekinumab was not with an elevated risk of TB compared with the general population in South Korea. They suggested that

TB screening is not required with ustekinumab treatment, even in areas with high disease burden. As a result, conducting comprehensive studies on biological agents beyond anti-TNF-α would prevent LTBI overdiagnosis and provide a better caliber of predictors such as OI-TST/IGRA.

There are several studies in the literature investigating the reliability and confirmation of TST and IGRAs. In a meta-analysis conducted by Rangaka et al. [23], in which 15 studies with a combined sample size of 26.680 were analyzed, a rate of 4-48 TB cases per 1.000 person-years was found for IGRA positive patients, and a rate of 2-24 TB cases per 1.000 person-years was found for TST-positive patients. The authors emphasized that both IGRAs and the TST lack high accuracy in predicting active TB infection, and IGRAs could potentially decrease the number of patients recommended prophylactic treatment in certain populations. In another meta-analysis, a rate of 3.7-84.5 TB cases per 1.000 person-years was found for IGRA-positive patients, and a rate of 2-32 TB cases per 1.000 person-years was found for IGRA-negative patients [24]. The authors mentioned that IGRAs could be a more suitable choice than the TST in nations where BCG is administered after infancy or administered repeatedly. Laffitte et al. [25] observed the LTBI in 20% of patients with psoriasis and maintained to prefer IGRA instead of the TST for screening. The authors remarked that even with accurate LTBI diagnosis and prophylaxis, the risk of active TB is continued during anti-TNF-α therapy. Several guidelines were published for screening LTBI before biologics, some of which propose TST or IGRA alone, some others recommend using both of them [26].

In a study, positivity of TST was investigated in elevated levels in patients with psoriasis than in the control group [9]. This difference was suggested to have a connection with an enhanced skin response to mycobacterial antigens as opposed to Koebner's phenomenon. They adjusted a 10 mm threshold value as a rational approach in patients before biologics to avoid overdiagnosis and unnecessary TB prophylaxis. Finally, they concluded that the in vitro QFT-plus test may be preferred over TST in psoriasis patients due to higher specificity and being unaffected by disease severity.

In our study, it was aimed to use the OI-TST/IGRA before the biologic therapies in psoriasis patients. As relying solely on either TST or IGRA is insufficient, in determining the risk of LTBI, it is also important to consider the risk factors such as contact with an active TB patient, having transplant or dialysis, and receiving an anti-TNF-α therapy [27]. As indicated in Table 1, these factors and more are taken into account in the OI-TST/IGRA. Although it is recommended to make certain calibrations in the risk calculation for these multifactorial agents, OI-TST/IGRA exhibits satisfactory proficiency in distinguishing individuals with a high or low risk of being diagnosed with active TB [28].

In the present study, PPV in patients with a previous diagnosis of positive LTBI was higher than LTBI-negative patients. However, OI-TST/IGRA did not show a significant difference between LTBI positive and negative patients for ARDATB and CRATB values (Table 3). TST size is a stronger determinant in calculating the PPV. On the other hand, the algorithm calculation utilized in OI-TST/IGRA primarily considers the presence of medical and radiographic risk factors as the key indicators of active disease risk when determining ARDATB and CRATB values. Therefore, the size of the TST reaction is with modest significance for them [8].

PPV and ARDATB values were significantly higher in patients with a TST size of> 15 mm than 5-9 mm and 10-15 mm (Table 3). Surucuoglu et al. [9] suggested that adopting a 10 mm cutoff value, irrespective of BCG vaccination, would be a suitable approach in patients before biological treatment to reduce the number of patients who may receive unwarranted prophylactic treatment for TB. However, analyzing TST reactions requires thinking in three dimensions; not only the size of the skin reaction but also PPV and risk of disease related to the medical and radiographic results of individuals [8].

This study showed that PPV, ARDATB, and CRATB values of QFT-GIT-positive and CXR-positive patients were significantly higher than QFT-GIT-negative and CXR-negative patients. QFT-GIT was emphasized in many studies to be used in psoriasis patients since it is not affected by the severity of disease and its in vitro application and higher specificity [29-32]. We also found that there was no significant correlation between QFT-GIT and TST. This

finding may also be significant to underline inadequate decision-making for screening LTBI based on TST.

The analysis of Tables 3 and 4 reveals that QFT-GIT results were more effective than TST results in previous LTBI decisions. Although LTBI decisions correlated with PPV, they did not correlate with ARDATB and CRATB values. This observation may serve as an indicator of the extent to which factors other than TST and QFT-GIT were considered in the previous decision-making process for LTBI. Considering both our study results and the calculation methods of OI-TST/IGRA, it becomes apparent that radiographic and medical factors have a stronger association with ARDATB and CRATB values. It is worth noting that TST and QFT-GIT exhibit a strong correlation with PPV, ARDATB, and CRATB values. In addition, QFT-GIT exhibit a closer correlation with PPV. Further studies on OI-TST/IGRA, in which multiple factors are taken into consideration, may establish cutoff values and deliver objective results for making more precise decisions in LTBI.

Based on the findings presented in Table 5, it can be concluded that being classified in the intermediate or high PPV group does not demonstrate a substantial impact on the positivity or negativity of the LTBI, TST, QFT-GIT, and CXR test results. The Kappa coefficients being close to zero and statistically insignificant indicate that the agreement is at the expected level of random agreement. In other words, there is no significant agreement between the PPV categories and the decisions of LTB, TST, QFTGT, and CXR tests.

In conclusion, retrospectively analyzing the LTBI screening results and LTBI diagnosis decisions with online OI-TST/IGRA, important inferences can be made. Firstly, TST size alone cannot be sufficient for the diagnosis of LTBI and active TB risk. In patients >5 mm size of TST, clinical and radiographic evaluation should be considered to maintain TB risk. TST size of >15 mm may be more relevant to increased risk. Secondly, QFT-GIT and CXR are strong parameters to determine the TB risk. Thirdly, OI-TST/IGRA showed overdiagnosis of LTBI, which was diagnosed by the guideline used for the present patients. Therefore, it is thought that ARDATB and CRATB values appear to be significant parameters in the estimation of TB risk. It seems feasible to prevent the occurrence of false positive outcomes and mitigate the overdiagnosis of LTBI by comprehensively assessing the combined results of OI-TST/IGRA.

It is worthwhile to focus on the diagnosis process of LTBI in a deductive manner, reviewing current valid tools, guidelines, and perceptions to check the state of affairs. According to the literature information, this study is the first, assessing the risk of active TB in patients with psoriasis before the biologics with online OI-TST/IGRA. OI-TST/IGRA may be a valuable tool in this issue and prevent overdiagnosis and unnecessary TB prophylaxis. The limitations of our study include the small number and diversity of patients, as well as the inability to determine cutoff values for OI-TST/IGRA values in diagnosing LTBI. Prospective studies with larger and more diverse groups will yield more precise and detailed results.

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References

1. Lande R, Botti E, Jandus C, et al. The antimicrobial peptide LL_{37} is a T-cell autoantigen in psoriasis. Nat Commun 2014;5:5621. https://doi.org/10.1038/ncomms6621
2. Raychaudhury SP. Recent advances in psoriasis: bench to bedside. Indian J Dermatol 2010;55:150. https://doi.org/10.4103/0019-5154.62749
3. Md Ms Duffin KC. Identifying and managing complications and comorbidities in patients with psoriasis. Semin Cutan Med Surg 2015;34:30-33. https://doi.org/10.12788/j.sder.2015.0135
4. Cataño J, Morales M. Isoniazid toxicity and TB development during biological therapy of patients with psoriasis in Colombia. J Dermatol Treat 2016;27:414-417. https://doi.org/10.3109/09546634.2016.1151857
5. Dilrukshi MDSA, Ratnayake CAP, Gnanathasan CA. Oral pyridoxine can substitute for intravenous pyridoxine in managing patients with severe poisoning with isoniazid and rifampicin fixed dose combination tablets: a case report. BMC Res Notes 2017;10:370. https://doi.org/10.1186/s13104-017-2678-6
6. Atikan BY, Cavusoglu C, Dortkardesler M, Sozeri B. Assessment of tuberculosis infection during treatment with biologic agents in a BCG-vaccinated pediatric population. Clin Rheumatol 2016;35:427-431. https://doi.org/10.1007/s10067-014-2842-5

7. Sellami M, Fazaa A, Cheikh M, et al. Screening for latent tuberculosis infection prior to biologic therapy in patients with chronic immune-mediated inflammatory diseases (IMID): Interferon-gamma release assay (IGRA) versus tuberculin skin test (TST). Egypt Rheumatol 2019;41:225-230. https://doi.org/10.1016/j.ejr.2018.11.003

8. Menzies D, Gardiner G, Farhat M, Greenaway C, Pai M. Thinking in three dimensions: a web-based algorithm to aid the interpretation of tuberculin skin test results. Int J Tuberc Lung Dis 2008;12:498-505.

9. Sürücüoğlu S, Türel Ermertcan A, Çetinarslan T, Özkütük N. The reliability of tuberculin skin test in the diagnosis of latent tuberculosis infection in psoriasis patients: a case-control study. Dermatol Ther 2020;33:e13496. https://doi.org/10.1111/dth.13496

10. Zhou G, Luo Q, Luo S, et al. Interferon-γ release assays or tuberculin skin test for detection and management of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis 2020;20:1457-1469. https://doi.org/10.1016/S1473-3099(20)30276-0

11. The Online TST/IGRA Interpreter. Available at: https://www.tstin3d.com/en/calc.html. Accessed 12 May 2023

12. Scolarici M, Dekitani K, Chen L, Sokol Anderson M, Hoft DF, Chatterjee S. A scoring strategy for progression risk and rates of treatment completion in subjects with latent tuberculosis. PLoS One 2018;13:e0207582. https://doi.org/10.1371/journal.pone.0207582

13. Özyurt K, Avcı A, Ertaş R, et al. PSORTAKSIS: a new psoriasis patient registry system used in dermatology clinic of Kayseri health training and research center. Turk J Dermatol 2018;12:23-27. https://doi.org/10.4274/tdd.3418

14. Alper S, Atakan N, Gürer MA, Onsun N, Özarmağan G. Updated turkish guidelines for the management of psoriasis with biologic agents. Turkderm-Turk Arch Dermatol Venereol 2010;44:105-112.

15. Cohen JR, Swerdlik ME, Phillips SM. Psychological testing and assessment. 3th ed. London: Mayfield, 1996.

16. Cohen J. A coefficient of agreement for nominal scales. Educational and Psychological Measurement 1960;20:37-46. https://doi.org/10.1177/001316446002000104

17. Bassukas ID, Gaitanis G, Constantopoulos SH. Diagnosis of tuberculosis in patients with psoriasis: the need for a modified approach. Eur Respir J 2011;38:231-232. https://doi.org/10.1183/09031936.00016611

18. Lee EB, Amin M, Man J, Egeberg A, Wu JJ. Rates of latent tuberculosis infection in patients treated with TNF inhibitors for psoriasis: a retrospective chart review. J Dermatol Treat 2018;29:671-675. https://doi.org/10.1080/09546634.2018.1443198

19. Nast A, Smith C, Spuls PI, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris – Part 1: treatment and monitoring recommendations. J Eur Acad Dermatol Venereol 2020;34:2461-2498. https://doi.org/10.1111/jdv.16915

20. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol 2019;80:1029-1072. https://doi.org/10.1016/j.jaad.2018.11.057

21. Elewski BE, Baddley JW, Deodhar AA, et al. Association of secukinumab treatment with tuberculosis reactivation in patients with psoriasis, psoriatic arthritis, or ankylosing spondylitis. JAMA Dermatol 2021;157:43-51. https://doi.org/10.1001/jamadermatol.2020.3257

22. Cho SI, Kang S, Kim YE, Lee JY, Jo SJ. Ustekinumab does not increase tuberculosis risk: results from a national database in South Korea. J Am Acad Dermatol 2020;82:1243-1245. https://doi.org/10.1016/j.jaad.2019.12.033

23. Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:45-55. https://doi.org/10.1016/S1473-3099(11)70210-9

24. Pai M, Denkinger CM, Kik SV, et al. Gamma ınterferon release assays for detection of mycobacterium tuberculosis infection. Clin Microbiol Rev 2014;27:3-20. https://doi.org/10.1128/CMR.00034-13

25. Laffitte E, Janssens JP, Roux Lombard P, et al. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-gamma release assay vs. tuberculin skin test. Br J Dermatol 2009;161:797-800. https://doi.org/10.1111/j.1365-2133.2009.09331.x

26. Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-639. https://doi.org/10.1002/acr.21641

27. Huaman MA, Sterling TR. Treatment of latent tuberculosis ınfection—an update. Clin Chest Med 2019;40:839-848. https://doi.org/10.1016/j.ccm.2019.07.008

28. Puyat JH, Shulha HP, Balshaw R, et al. How well does TSTin3D predict risk of active tuberculosis in the canadian ımmigrant population? An external validation study. Clin Infect Dis 2021;73:3486-3495. https://doi.org/10.1093/cid/ciaa780

29. Megna M, Ferrillo M, Ruggiero A, Cinelli E, Gallo L, Fabbrocini G. QuantiFERON TB-gold conversion rate among psoriasis patients under biologics: a 9-year retrospective study. Int J Dermatol 2021;60:352-357. https://doi.org/10.1111/ijd.15217

30. Karataş Toğral A, Muştu Koryürek Ö, Şahin M, Bulut C, Yağci S, Ekşioğlu HM. Association of clinical properties and compatibility of the QuantiFERON-TB Gold In-Tube test with the tuberculin skin test in patients with psoriasis. Int J Dermatol 2016;55:629-633. https://doi.org/10.1111/ijd.12973

31. Akdogan N, Dogan S, Gulseren D, et al. Serial Quantiferon-TB Gold test results in 279 patients with psoriasis receiving biologic therapy. Dermatol Ther 2021;34:e14699. https://doi.org/10.1111/dth.14699

32. Tsiouri G, Gaitanis G, Kiorpelidou D, et al. Tuberculin skin test overestimates tuberculosis hypersensitivity in adult patients with psoriasis. Dermatology 2009;219:119-125. https://doi.org/10.1159/000222431

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Author contributions

Designing the study and writing the first draft manuscript were performed by ZM, K.O., M.A., E.G.Y., R.E. and O.G. Data collection was performed by K.O., M.A., E.G.Y. and R.E. Material preparation was performed by Z.M., K.O., M.A., E.G.Y. and R.E. Analysis was performed by O.G. All authors provided critical feedback throughout the study, reviewed and edited subsequent drafts and approved the final draft.