Original Investigation / *Özgün Araştırma*

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Diagnostic Value of Interferon-Gamma Release Assay in the Diagnosis of Tuberculosis Infection Before the Use of TNF-Alpha Blocker in Pediatric Rheumatology Patients

Pediyatrik Romatoloji Hastalarında Tüberküloz Enfeksiyonu Tanısında TNF-Alfa Blokörü Kullanımı Öncesi İnterferon-Gama Salınım Testlerinin Tanısal Değeri

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Abstract

Objective: In rheumatic diseases, it has been reported that the risk of developing tuberculosis increases 1.6 to 25.1 times after the use of tumor necrosis factor-alpha (TNF-α) blocker treatment. Therefore, latent tuberculosis infection is very important in patients who use TNF-α blocker drugs. In this study, it was aimed to investigate the diagnostic value of interferon-gamma release assay before TNF-α blocker therapy in the diagnosis of latent tuberculosis infection in pediatric patients with chronic inflammatory disease resistant to standard treatments and with TNF-indication.

Material and Methods: In this study, 93 pediatric patients with chronic rheumatic inflammatory disease, who would be started on anti-TNF therapy and investigated for latent tuberculosis infection, and 69 control patients without chronic disease, who were examined for any reason, were retrospectively analyzed. QuantiFERON-TB Gold Plus test, which is a commercial test based on interferon-gamma QuantiFERON-ELISA technique, and tuberculin skin test were applied to all patients examined.

Results: In the patient group examined in this study, 19 (20.4%) of 93 patients were positive for tuberculin skin test and four (4.3%) for interferon-gamma release test. There were 17 (18.2%) patients with positive tuberculin skin test results and negative interferon-gamma release test results, and two (2.2%) patients with negative tuberculin skin test results

Öz

Giriş: Romatizmal hastalıklarda, tümör nekrozis faktör-alfa (TNF-α) blokörü ilaç kullanımı sonrasında tüberküloz gelişme riskinin 1.6-25.1 kat arttığı bildirilmiştir. Bu nedenle, TNF-α blokörü ilaçları kullanacak hastaların latent tüberküloz enfeksiyonu gelişim riski açısından taranması büyük önem taşımaktadır. Bu araştırmada kronik romatizmal enflamatuvar hastalığa sahip, standart tedavilere dirençli, TNF-α blokörü kullanım endikasyonu olan çocuk hastalarda, latent tüberküloz enfeksiyonu tanısında, TNF-α blokörü tedavisinden önce interferon-gama salınım testlerinin tanısal değerini araştırmayı amaçladık.

Gereç ve Yöntemler: Bu araştırmada, kronik romatizmal enflamatuvar hastalığı bulunan, TNF-α blokörü kullanımı endikasyonu olan latent tüberküloz enfeksiyonu açısından araştırılan 93 çocuk hasta ve kronik hastalığı olmaksızın herhangi bir nedenle muayene olan 69 kontrol hastası retrospektif olarak incelendi. İncelenen tüm hastalara interferon-gama araştırmasına dayalı testlerden ELISA tekniğine dayalı ticari bir test olan QuantiFERON-TB Gold Plus testi ve tüberkülin deri testi uygulanmıştır.

Bulgular: Bu araştırmada incelenen hasta grubundaki 93 hastanın 19 (%20.4)'unun tüberkülin deri testi, dördünün (%4.3) interferon-gama salınım testi sonucu pozitif olarak saptandı. Tüberkülin deri testi pozitif, interferon-gama salınım testi sonucu negatif olan 17 (%18.2) hasta, tüberkülin deri testi negatif, interferon-gama salınım testi sonucu pozitif

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and positive interferon-gamma release test results. There were two (2.2%) patients with positive interferon-gamma release test and tuberculin skin test. Tuberculin skin test was negative in all 69 patients in the control group, and interferon-gamma release assay results were positive in three (4.3%) of them. In this study, the agreement between the tuberculin skin test and the interferon-gamma release assay was found to be weak (p< 0.01). Isoniazid prophylaxis was started before biologic agent treatment in 19 (%20.4) patients whose tuberculin skin test was found to be 5 mm and above in 93 patients who were screened with tuberculin skin test and interferon-γ release assay. No active tuberculosis development was detected in the 2.5-year follow-up of 19 patients who were included in the study and diagnosed with latent tuberculosis infection.

Conclusion: All patients planned to receive TNF-alpha blockers should be screened for tuberculosis before treatment. In the light of current guidelines, patients should be screened for tuberculosis infection with contact history, symptoms, physical examination, chest X-ray, and tuberculin skin test and/or interferon gamma release assay. Although some studies have shown that IGST may be more useful for LTBI screening before TNF-α blocker treatment, this conclusion could not be reached in our study either.

Keywords: Interferon-gamma release assay, tuberculin skin test, tuberculosis infection, tumor necrosis factor-α blocker

olan iki (%2.2) hasta, hem interferon-gama salınım testi ve hem de tüberkülin deri testi pozitif olan iki (%2.2) hasta saptandı. Kontrol grubundaki 69 hastanın tamamında tüberkülin deri testi negatif, üçünde (%4.3) interferon-gama salınım testi sonucu pozitif idi. Bu çalışmada, tüberkülin deri testi ve interferon-gama alınım testi arasındaki uyum zayıf olarak saptandı (p< 0.01). Tüberkülin deri testi ve interferon-gama salınım testi ile taranan 93 hastanın tüberkülin deri testi 5 mm ve üzeri saptanan 19 (%20.4) hastaya biyolojik ajan tedavisi öncesi izoniyazid profilaksisi başlanmıştı. Araştırma sürecinde çalışmaya alınan ve latent tüberküloz enfeksiyonu tanısı alan 19 hastanın 2.5 yıllık izlemlerinde aktif tüberküloz gelişimi saptanmadı.

Sonuç: TNF-α blokörü alması planlanan tüm hastalara mutlaka tedavi öncesinde tüberküloz taraması yapılmalıdır. Hastalar güncel kılavuzlar ışığında temas öyküsü, semptomlar, fizik muayene, akciğer grafisi ve tüberkülin deri testi ve/veya interferon gama salınım testiyle tüberküloz enfeksiyonu açısından taranmalıdır. Yapılan bazı çalışmalarda IGST'nin TNF-α blokörü tedavisi öncesinde LTBE taraması için daha yararlı olabileceği gösterilse de bizim çalışmamızda bu sonuca varılamamıştır.

Anahtar Kelimeler: İnterferon-gama salınım testleri, tüberkülin deri testi, tüberküloz enfeksiyonu, tümör nekrozis faktör-α blokörü

Introduction

In recent years, understanding the pathogenesis of rheumatological diseases has enabled the use of biological agents in the treatment of these diseases. The most commonly used of these agents are TNF-α blockers, which antagonize the biological activities of tumor necrosis factor-alpha (TNF-α). TNF-α is a proinflammatory cytokine that plays a role in the pathogenesis of many inflammatory diseases and is responsible for granuloma formation and continuity in granulomatous diseases, especially tuberculosis (TB). The use of TNF-α blocking drugs may lead to the inhibition of granuloma formation, resulting in reactivation of latent tuberculosis infection (LTBI) and/or active tuberculosis (1,2). It has been shown that the risk of developing TB increases 1.6-25.1 times during or after the use of TNF-α blocker drugs (3). Therefore, it is recommended that patients with indications for use of TNF-α blockers should be screened for the risk of developing LTBI (3,4). Currently, two different tests are used in the diagnosis of LTBI: tuberculin skin test (TDT) for 100 years and interferon-gamma release tests (IGST) for the last 20 years (5). The presence of the antigen used in TST in non-tuberculous mycobacteria (NTBM) and BCG vaccine origin reduces the specificity of the test. It has been reported that the specificity of TST in BCG-vaccinated patients is between 65-70% (6). In addition, TST can lead to false-negative results in common and severe forms of the disease such as miliary TB and in cases such as the use of immunosuppressive drugs (6).

The antigens used in IGST are specific to *Mycobacterium tuberculosis* complex and are encoded by genes located at the RD1 locus of bacterial DNA. These antigens are not found in NTBM and BCG vaccine origin except *Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium szulgai* and *Mycobacterium flavescens* and are not affected by BCG vaccine (7-11). Although different results have been reported among studies published on interferon-gamma (IFN-γ) release tests, the strongest and most consistent finding is the high specificity of IGST, especially in BCG-vaccinated children and in countries with low TB incidence (12,13). Especially in countries where the incidence and prevalence of TB is high, LTBI reactivation poses an important problem in the treatment with TNF-α blocking biological agents. Therefore, LTBI and active TB disease should be excluded before TNF-α blocker therapy is started in this group of patients (14).

In this study, it was aimed to investigate the diagnostic value of IGST and TST in the diagnosis of LTBI before the use of TNF-α blocker agents in pediatric patients with chronic rheumatic inflammatory disease, resistant to standard treatments, and TNF-α blocker use.

Materials and Methods

Study Group

In this study, 93 pediatric patients who were followed up with the diagnosis of chronic rheumatic inflammatory disease in the Department of Pediatric Rheumatology of Çukurova University between March 1, 2007 and June 30, 2019, did not respond to standard treatments and had indications for starting TNF-α blocker therapy (Group 1: Patient Group) and 69 healthy children (Group 2: Control Group) of similar age and sex, who were screened for tuberculosis for any reason, were examined. Patients who underwent IGST and TST for latent TB screening before TNF-α blocker treatment were retrospectively screened and included in the study. The study was approved

by the Çukurova University Ethics Committee (March 8, 2019-86). Socio-demographic status and medical histories of the patients, vaccination cards, BCG vaccination histories, BCG scar counts, tuberculosis-related symptoms, physical examination findings, family scans, radiological imaging, treatments received by the patients and duration of treatment were recorded in the research sheets from patient files. In the control group, demographic data, vaccination cards, BCG vaccination history and BCG scar counts were recorded. In both groups, TB contact history was recorded in research sheets. Close contact was defined as living in the same house with the source case and/or spending eight hours or more in the same room and remote emote contact was defined as living in a different house with the source case and/or spending less than one hour in the same room once a week (15). BCG vaccinations of the patients who did not have a BCG scar record in the physical examination in patient files were confirmed with vaccination cards and the vaccination tracking system (ATS). Chest X-rays were taken, and IGST and TST tests were performed in all of the patient and control groups. Findings of the patients who had lung computed tomography (CT) were recorded. TST was performed by experienced healthcare personnel on the volar face of the left forearm with a tuberculin injector intradermally using 0.1 mL, 5TU PPD (Tuberculin Mammalian 80, Sofia, Bulgaria) solution, and the transverse diameter of the induration formed 72 hours after the application was measured. TST was considered positive in those vaccinated with BCG if the result was 15 mm and above, in those without BCG vaccinated, TDT was considered positive if the reulst was 10 mm and above, and in immunocompromised individuals, 5 mm and above was considered positive. QuantiFERON-TB Gold Plus (QFT-Plus) (QIAGEN Bioinformatics, Hilden, Germany), a commercial kit based on the ELISA technique, was applied to the patients included in the study.

Statistical Analysis

Categorical measurements were evaluated as numbers and percentages, and numerical measurements were evaluated as mean and standard deviation (median and minimum-maximum where necessary). Chi-square test was used to compare categorical measures between the groups. The agreement between TST diameter and IGST results was examined by the kappa coefficient. Compliance of numerical measurements with normal distribution was tested with Kolmogrov Smirnov test. Mann-Whitney U test was used to compare the non-normally distributed numerical measurements between the two groups. IBM SPSS Statistics Version 20.0 package program was used in the statistical analysis of the data (16). Statistical significance level was taken as 0.05 in all tests (17).

Results

Of the 93 patients with chronic rheumatic inflammatory disease included in the study, 69 (74.2%) were diagnosed with juvenile idiopathic arthritis (JIA), one (1.1%) with JIA, familial Mediterranean fever (FMF) and uveitis, four (4.3%) with JIA and FMF, 10 (10.7%) with JIA and uveitis, six (6.4%) with autoimmune uveitis, two (2.2%) with adenosine deaminase-2 (ADA-2) deficiency, and one (1.1%) with vasculitis. Of the patients diagnosed with JIA, eight (8.6%) had systemic JIA, 11 (11.8%) rheumatoid factor (RF) negative JIA, two (2.2%) RF positive JIA, 25 (26.9%) oligoarticular JIA. Nine (9.7%) patients were diagnosed with HLA B27 (-) enthesitis associated arthritis, 13 (13.9%) with HLA B27 (+) enthesitis associated arthritis, and one (1.1%) with juvenile psoriatic arthritis.

Demographic and clinical characteristics of the patients are shown in Table 1. Of the patients, 39 (41.9%) were males and 54

Table 1. Patients belonging demographic and clinic features

Features	Descriptive statistics
Age (years)[a]	11.6 ± 4.3 12.0 (1.5-18.0)
Gender[b]	
Female	54 (58.1)
Male	39 (41.9)
Age at diagnosis (years)[a]	8.3 ± 4.7 8.0 (1.0-16)
Growth parameters[b]	
<5th percentile (height)	9 (9.7)
<5 percentile (kg)	9 (9.7)
Patient follow-up period after biological agent (months)[b]	33.0 (2.0-144.0)
≤12	9 (9.7)
13-24	19 (20.4)
25-72	46 (49.5)
>72	19 (20.4)
TNF-α blocker used[b]	
Etanercept	62 (66.6)
Adalimumab	26 (28)
Infliximab	5 (5.4)
Symptoms[b]	
Cough	7 (7.5)
Sputum	2 (2.2)
Fire	1 (1.1)
Weight loss	0 (0)
Night sweats	2 (2.2)
Joint pain	38 (40.9)
History of tuberculosis contact (+)[b]	6 (6.4)
MTX usage (+)[b]	87 (93.5)
Prednol use (+)[b]	34 (36.5)

[a]Values are given as mean ± standard deflection and as median (min-max).
[b]Values are given as n (%).

(58.1%) were females, with a mean age of 11.6 ± 4.3 years, and 8.3 ± 4.7 years at the time of diagnosis. In 9.7%, the height and weight percentile values for age were below 5%. All of the patients had a history of vaccination and 82 (88.2) had vaccination scars. Mean follow-up period of the patients was 33 months, and the most commonly used TNF-α blocker was etanercept with 66.6%. Cough was present in 7.5% of the patients.

In the control group, 29 (42%) of the patients were males and 40 (58%) were females, with a mean age of 10.58 ± 4.05 years. There was no statistically significant difference between the patient and control groups in terms of age and sex (p= 0.127, p= 0.990, respectively).

The treatments received by the patients before TNF-α blocker treatment are shown in Table 2. Demographic and clinical data according to TST and IGST values are shown in Table 3.

Table 2. Treatments received by the patients prior to the biological agent

Treatment	Drugs used before TNF-α blocker, n (%)
Prednisolone	34 (36.6)
Methotrexate	87 (93.5)
Salazopyrine	12 (12.9)
Azathioprine	4 (4.3)
Mycophenolate	2 (2.2)
Ciclosporin	1 (1.1)

Table 3. Demographic and clinical data according to TST and IGST values

Characteristics	TST (+) (n= 19)	TST (-) (n= 74)	P	IGST (+) (n= 4)	IGST (-) (n= 89)	p
Age (year)[a]	12.6 ± 4.4 12 (3-18)	11.2 ± 4.3 12 (1.5-18)	0.242	13 ± 5.2 14.5 (6-17)	11.4 ± 4.3 12 (1.5-18)	0.469
Sex[b]						
Male	8 (19.5)	33 (80.5)	>0.999	3 (7.3)	38 (92.7)	0.312
Female	11 (20.4)	43 (79.6)		1 (1.9)	53 (98.1)	
Weight[b]						
<%5	3 (33.3)	6 (66.7)	0.382	0 (0)	9 (100)	>0.999
≥%5	16 (19.0)	68 (81.0)		4 (4.8)	80 (95.2)	
Height[b]						
<%5	3 (33.3)	6 (66.7)	0.382	0 (0)	9 (100)	>0.999
≥%5	16 (19.0)	68 (81.0)		4 (4.8)	80 (95.2)	
Contact history[b]						
Yes	1 (16.7)	5 (83.3)	>0.999	0 (0.0)	6 (100.0)	>0.999
No	18 (20.2)	71 (79.8)		4 (4.5)	85 (95.5)	
Diagnosis[b]						
JIA	17 (20.2)	67 (79.8)	>0.999	4 (4.8)	80 (95.2)	>0.999
Non-JIA	2 (22.2)	7 (77.8)		0 (0.0)	9 (100.0)	
PAAC graphy[b]						
Normal	17 (18.7)	74 (81.3)	**0.040***	3 (3.3)	88 (96.7)	0.085
Positive	2 (100.0)	0 (0.0)		1 (50.0)	1 (50.0)	
MTX use[b]						
Yes	19 (21.8)	68 (78.2)	0.340	4 (4.6)	83 (95.4)	>0.999
No	0 (0.0)	6 (100.0)		0 (0.0)	6 (100.0)	
Prednol use[b]						
Yes	7 (20.0)	28 (80.0)	>0.999	2 (5.9)	32 (94.1)	0.621
No	12 (20.0)	48 (80.0)		2 (3.4)	57 (96.6)	

[a]Values given as mean ± standard deviation and median (min-max).
[b]Values given as n (%).
*p≤ 0.05.

There was no statistical difference between TST and IGST positivity and age (p= 0.242, p= 0.469, respectively).

BCG vaccination times were categorized as <5 years, 5-10 years, >10 years. There was no statistically significant difference between BCG vaccination time and TST and IGST results (p= 0.562 and p= 0.821, respectively). Of the 93 patients examined, six (6.5%) had contact with a TB patient, one (1.1%) was in close contact and five (5.4%) was in distant contact. There was no statistically significant difference between TB contact history and TST and IGST positivity. No statistically significant correlation was found between patients with JIA and non-JIA patients, and TST and IGST positivity (p> 0.999 and p> 0.999, respectively).

While there was a statistically significant difference between the findings on chest X-ray and TST positivity (p= 0.040), there was no significant difference between IGST positivity and chest X-ray findings (p= 0.085). While TST was positive in two (100%) of two patients with chest X-ray findings, chest radiography findings of all patients with negative TST were found to be normal. X-ray findings of patients with chest X-ray were consistent with perihilar infiltration.

There was no statistically significant difference between the patients' methotrexate (MTX) and prednisolone use and TST and IGST positivity (p> 0.999 and p> 0.621, respectively).

When TST and IGST results of the 93 patients included in the study were evaluated together, the TST results of 19 were positive and the IGST results of four of them were positive. While 17 patients with positive TST results and negative IGST results were detected, two patients with negative TST results and positive IGST results were identified. The number of both TST positive and IGST positive patients was two. There was no statistically significant difference between TST and IGST (p= 0.253).

Isoniazid (INH) prophylaxis was started before the biological agent in 19 (20.4%) patients who were screened with TST and whose results were positive. TST negative and IGST positive two patients were evaluated with physical examination, history, clinical findings, chest X-ray findings, and prophylaxis was not initiated. LTBI or active tuberculosis did not develop in the follow-up of these three patients, and the patients are still under follow-up by us. No active TB development was detected in the 2.5-year follow-up period of 19 patients diagnosed with LTBI.

TST results of all patients in the control group were negative. IGST results of three patients were positive. Chest radiographs of these patients were normal, LTBI or active tuberculosis did not develop in the follow-up, and the patients are still under follow-up by us.

In the family screening of 93 patients examined, 378 people were included. TST result was negative (<15 mm) in 324 (85.7%) of the people who were screened, and positive (≥15 mm) TST result in 54 (14.3%) of them. Active tuberculosis infection was not detected in patients with positive TST results.

In Figure 1, the compatibility of TST and IGST tests according to age groups of the patients in Group 1 and Group 2 were examined.

Groups 1 and 2 were divided into 2 subgroups as those under 15 years of age and those at and over 15 years of age, and the compatibility between the two tests was evaluated.

The compliance of both tests was poor in the patient (Group 1) and control (Group 2) groups under the age of 15 (n= 121) and in individuals aged 15 and over (n= 41) (Figure 1).

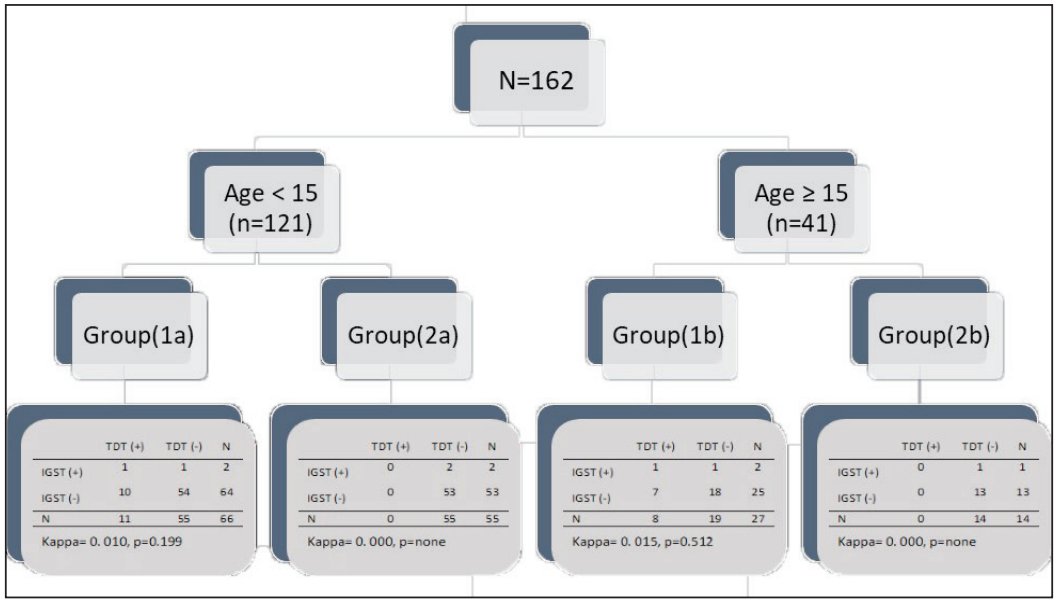

Figure 1. Compatibility between TST and IGST by age of individuals in the patient and control groups.

Group 1a was divided into subgroups as the patient group under the age of 15 years, Group 2a as the control group under the age of 15 years, Group 1b as the patient group aged 15 years and above, and Group 2b as the control group aged 15 years and above.

Discussion

After the use of TNF-α antagonists in the treatment of chronic inflammatory diseases, an increase in the incidence of TB was detected in this patient group as a result of immunological influence. TB cases associated with TNF-α antagonists are frequently seen as extrapulmonary or diffuse infections (18). TB infections appear either in the form of LTBI shortly after the initiation of TNF-α antagonists or in the form of new TB infection during further treatment.

Because of the risk of developing LTBI, patients with indications for use of TNF-α blockers should be screened for LTBI before starting TNF-α blocker therapy (19). According to the Rheumatology Research Education Association (RAED) Guideline, it is recommended to start INH prophylaxis in patients with positive IGST result as well as in patients with a TST result of ≥5 mm (20-22).

In a study conducted in our country, 115 patients, all of whom received BCG-vaccinated anti-TNF therapy, have been included in the study. IGST has been performed in 10 of these patients, and the IGST result has been found positive in one of these 10 patients (23). In our study, however, we found that 4.3% of all BCG-vaccinated patients had a positive IGST result and 20.4% had a positive TST result. The agreement of both tests was 11% when the TST cut-off value was taken as 5 mm, and 5% when the TST cut-off value was taken as 10 mm, and the agreement of both tests was poor. It is considered that the low number of patients with positive IGST values in our study group affected the statistical results negatively.

In studies, it has been reported that the prophylaxis indication for LTBI before the use of TNF-α blockers is higher when TST results are taken into account (24,25). Many experts recommend that TST and IGST tests be performed for patients with risk factors for LTBI, and that preventive treatment for LTBI should be started, whichever test is positive, after TB disease is excluded (24-27).

In a study conducted in Türkiye, 49 of 97 patients have had positive TST results and 10 of them have been found IGST positive, and INH prophylaxis has been started in all patients (28). In our study, TST value was positive in 19 (20.4%) of 93 patients screened with both tests, and IGST test was positive in two (10.5%) of these patients, and INH prophylaxis was started in all TST-positive patients.

In terms of TDT negative people, IGST tests are recommended for those with a high risk of LTBI, those at risk of progression to tuberculosis, people infected with human immunodeficiency virus (HIV), and if there is clinical suspicion for TB disease. Considering that false negativity in TST and IGST may occur in immunocompromised patients with chronic disease, it has been reported that INH prophylaxis should be started when positivity is detected in any of them (23). In patients with a positive IGST result, further examination should be performed and the signs and symptoms of tuberculosis disease should be investigated, *M. tuberculosis* infection should be diagnosed and infection treatment should be recommended. In addition, incorrect blood collection, analysis error, delay in processing, immunomodulation, etc. It should be noted that their condition affects the IGST result. Our study is retrospective, and INH prophylaxis was not initiated in two patients with positive IGST test results and negative TST, and it was determined that active TB development was not observed in these patients during their follow-up. These patients were followed up with chest X-ray, TST and IGST at three-month intervals throughout the study and are still under follow-up by us.

When the relation between TST and IGST results and sex is examined, variable results have been reported in the literature. In a study conducted in Spain, the rate of TST and IGST positivity has been found to be higher in adult male patients. The reason for this situation was thought to be more frequent contact with tuberculosis patients due to the greater participation of men in social life. In addition, in the mentioned study, the rate of TST and IGST positivity has been found to be higher in patients over 55 years of age (29). In our study, we did not find a significant difference between TST and IGST results and sex. However, since the population of our study was pediatric patients, the fact that their social environment was similar (mostly school and family) may explain this situation. At the same time, when the relationship between TST and IGST results and age was evaluated in our study, no statistically significant difference was found. In the study conducted in the adult patient group, it can be thought that there is a statistically significant difference, since the age range is wider than the pediatric patient group. Since our study was conducted in the pediatric age group, it can be thought that there is no significant difference between the TST and IGST results and age.

In a study conducted in Poland in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) patients, IGST and TST tests have been compared in terms of tuberculosis screening before anti-TNF treatment. Ninety AS and RA patients and 20 control patients were included in the study and all patients have been selected from patients who had BCG vaccine. TST positivity limit value was taken as 5 mm in the patient group and 10 mm in the control group. TST positivity rate was 28.9% in the patient group and 55% in the control group. IGST positivity rate was 22.2% in the patient group and 20% in the control group. In the patient group, the rate of patients with both

tests positive was 16.7%, and the rate of patients with both tests negative was 62.2% (30). Although the rate of patients in which both tests were negative in this study was similar to our study, the rate of patients who were positive was found to be lower in our study.

In a study conducted in Türkiye investigating the incidence of tuberculosis infection in patients using anti-TNF, the rate of patients with normal chest X-ray has been found to be 74.9% (31). In our study, we found this rate to be 89.5%. In our study, when TST and IGST results were compared with chest X-ray findings, a significant correlation was found between TST positivity and chest X-ray findings (p= 0.040). The same correlation was not found between IGST and pulmonary findings (p= 0.085). In addition, while TST was positive in two (100%) of two patients with chest X-ray findings; chest radiography findings of all patients with negative TST were found to be normal.

In our study, no tuberculosis development was detected in the follow-up of the patients who were started on anti-TNF therapy.

As a result, it is difficult to determine the sensitivity and specificity of IGST because there is no gold standard test for the diagnosis of LTBI. Although some studies have shown that IGST may be more useful for LTBI screening before TNF-α blocker treatment, this conclusion could not be reached in our study either. Long-term and multicenter prospective studies are needed to determine the rate of TB reactivation in patients diagnosed with LTBI by TST and IGST, and to determine the sensitivity and specificity of the tests.

Ethics Committe Approval: Ethics committee approval for the study was obtained from Çukurova University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (Decision no: 03, Date: 08.03.2019).

Informed Consent: Patient consent was obtained.

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