Volume 9, Issue 6, 2019, 4485 - 4493 ISSN 2069-5837

Biointerface Research in Applied Chemistry

www.BiointerfaceResearch.com

https://doi.org/10.33263/BRIAC96.485493

Original Research Article Open Access Journal

Received: 08.09.2019 / Revised: 18.10.2019 / Accepted: 19.10.2019 / Published on-line: 21.10.2019

An updated systematic review on the applied TST and IGRA Test for diagnosing LTBI in patients treated with TNF-α inhibitor drugs

Samane Hozeifi [1], Farshid Abedi [2], Hossein Beydokhti [3], Tahereh Farkhondeh [4], Saeed Samarghandian [5], Elham Atabati [1,*]

[1]Department of Internal Medicine, School of Medicine, Clinical Resaerch Development Unit (CRDU), Valiasr Hospital, Birjand University of Medical Sciences, Iran
[2]Infectious Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran
[3]Instructor of Medical Librarianship and Information Sciences, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[4]Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand. Iran
[5]Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran

*corresponding author e-mail address: **Elham1405@yahoo.com** |Scopus ID 35739718800

ABSTRACT

Present systematic review was designed to compare the efficacy of interferon-γ release assays (IGRAs) and tuberculin skin test (TST) for diagnosing latent tuberculosis infection (LTBI) in patients subjected to the anti-TNF-α therapy. The MEDLINE (Ovid), PubMed, Embase, Scopus, Cochrane library, and Web of Science ISI databases were searched for selecting studies to compare the efficiency of IGRAs [QuantiFERONTB Gold (QFT-GT), QuantiFERON-TB Gold In-Tube (QFT-GIT)and T-SPOT.TB] and TST in patients under the anti-TNF-α therapy. After evaluating all studies, we systemically reviewed the results of 37 studies with a total sample size of 8584 patients. The agreement between IGRASs and TST was poor to moderate, however, the anti-TNF-α therapy mostly decreased the percentage of this agreement. BCG vaccination could cause false results of TST assay. The developed active TB in patients with IGRAs positive results during follow-up showed lower than TST positive patients. In conclusion, in the treated patients with anti-TNF-α with previous BCG vaccination, IGRAs might be the better assay to diagnosis LTBI by reducing the false results rate in comparison with the TST. However, more investigations should be done to compare the advantage of IGRAs with conventional test in the treated patients with TNF-α antagonists.

Keywords: *anti-TNF-α drug; latent tuberculosis; QuantiFERON; tuberculin skin test*

1. INTRODUCTION

Tuberculosis is a serious bacterial disease that is important cause of morbidity and mortality worldwide [1]. Tuberculosis is caused by Mycobacterium tuberculosis bacteria (MTb) [1]. Tuberculosis mostly occurs in latent form and does not cause any symptoms, however, 10 % of cases may change to active form with classic symptoms of tuberculosis. Several factors such as HIV, chronic lung diseases, smoking, alcoholism, malnutrition, diabetes mellitus, and certain drugs such as TNF-α antagonists are responsible for stimulation of latent form of tuberculosis [2]. TNF-α inhibitors are prescribed for the patients with several rheumatic diseases [rheumatoid arthritis (RA), spondyloarthropathies (ankylosing spondylitis (AS) and psoriasis arthritis (PsA), and juvenile idiopathic arthritis (JIA)], inflammatory bowel disease (IBD) and undifferentiated connective tissue disease (UCTD) [3]. It was indicated that TNF-α has the main effect on the formation and preservation of granuloma, and TNF-α inhibitor drugs lead to the dissociation of the granuloma and dispersion of M. tuberculosis [4]. The risk of development of latent tuberculosis to active form would elevate by TNF-α inhibitor drugs [4]. Therefore, it is important to recognition patient with latent tuberculosis before to anti-TNF-α medication [4]. There is no suitable method with gold standard for discernment of latent tuberculosis infection (LTBI) [5]. Till now, tuberculin skin test (TST) is mostly used for diagnosing LTBI. TST test is based on a "delayed hypersensitivity response" of infected patient to MTb [6]. However, there are several limitations for the TST that affect on findings of the test and cause false-positive results, including "Bacille Calmette-Guerin (BCG)" vaccine, and also corticosteroid therapy causes false-negative results [6]. Todays, "interferon-γ release assays (IGRAs)" have introduced as an alternative for TST [7]. IGRAs including QuantiFERON-TB Gold in Tube (QFTGIT), QuantiFERON-Gold (QFTG) and T-SPOT.TB (TS.TB) assess the immune response to TB-specific antigens on lymphocytes [7]. The QFT-GT, a novel version of QuantiFERON assay, assesses the interferon (IFN)-γ release from induced blood in response to antigens by an "enzyme-linked immunosorbent assay (ELISA)" [8]. Today, TS.TB, a fourth-generation "QuantiFERON TB Gold Plus", has been used to assess peripheral blood mononuclear cells by ELISA method [9]. Results of IGRAs may be indeterminate due to failure of IFN-γ production following stimulation with a strong mitogen [9]. T-cell dysfunction or technical mistake leads to indeterminate results [9]. Additionally, rheumatic patients prior anti-TNF-α therapy usually were under other immunosuppressive therapy (IST) including steroid that may affect the results of tests [5]. Until now, there are very few reviews evaluating TST and IGRA tests for detecting Latent TB in patients treated with TNF-α inhibitor drugs. The aim of this investigation was to evaluate LTBI diagnostic tests specifically in patients treated with TNF-α inhibitor drugs by a systematic review of available studies.

2. MATERIALS AND METHODS

Methods.

The present systematic study was done based on the "Preferred Reporting Items for Systematic Reviews (PRISMA) guideline".

Search strategy and study selection.

PubMed, Embase, MEDLINE (Ovid), Cochrane Library, Scopus, and Web of Science ISI databases were searched by for selecting articles between 1966 and January 2019. The following items were used as keywords ("Tuberculin skin test" OR "Tuberculin Test OR "BCG Vaccine" OR "Mycobacterium tuberculosis" OR "Tuberculin" OR "Mantoux test" OR "TB skin test" OR "TB test" OR "PPD skin test" OR "PPD test" OR "TB Screening"OR "high tuberculosis incidence setting" OR "TB-endemic population") OR ("Interferon gamma Release" OR "Interferon-gamma Release" OR "QuantiFERON" OR "IGRAs" OR "Interferon-gamma" OR "Interferon-gamma Release Tests" OR "T-SPOT.TB" OR "QuantiFERON-TB Gold") AND ("Latent tuberculosis infection" OR "latent TB" OR "Latent tuberculosis" OR "Tuberculosis" OR "Latent Tuberculosis") AND ("Tumor Necrosis Factor alpha" OR "TNFalpha" OR "TNF alpha" OR "Tumor Necrosis Factor-alpha" OR "Certolizumab Pegol" OR "Infliximab" OR "Adalimumab" OR "Anti-tumor necrosis alpha" OR "PEG-modified tumor necrosis factor-alpha" OR "isotryptoquivaline F" OR "Anti-TNF-alpha" OR "Biological Therapy" OR "Antirheumatic Agents" OR "Adalimumab" OR "Golimumab" OR "Immunosuppressive Agents" OR "Etanercept") . First, independent articles to our strategy were removed from this study according to the titles and abstracts. Then, the full text of selected articles was reviewed and matched articles with the inclusion criteria were included in the study. In addition, the reference lists of each selected paper were assessed for any omitted article. Finally, English language papers that evaluated the sensitivity and efficiency of commercial IGRAs and TST for diagnosing LTBI in patients under TNF-α inhibitor therapy were included.

Data extraction.

Three reviewers collected data in **table** 1 including the first author, published country and year, patients number, type of rheumatic disease "(Rheumatoid arthritis (RA), Ankylosing Spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD), undifferentiated connective tissue disease (UCTD), psoriasis**,** demographic characterization (including gender, age and BCG vaccination), TNF-α inhibitors (infliximab, adalimumab, golimumab, certolizumab, etanercept), IGRA and TST methods ".

3. RESULTS

Study selection.

The literature search yielded 2067 citations; 1165 citations obtained after deleting duplicate papers. 218 studies selected following evaluating title and abstract. English language, using TNF-α blockers, and using both IGRA and TST were the inclusion criteria. (Figure 1). 36 studies were found that considered our inclusion criteria. All these studies used both TST and QuantiFERON tests (10 QFT-GT and 17 QFT-GIT) [10-35] before TNF-α inhibitor therapy. The ten of these papers evaluated both QFT and T-SPOT.TB or T-SPOT.TB [36-45].

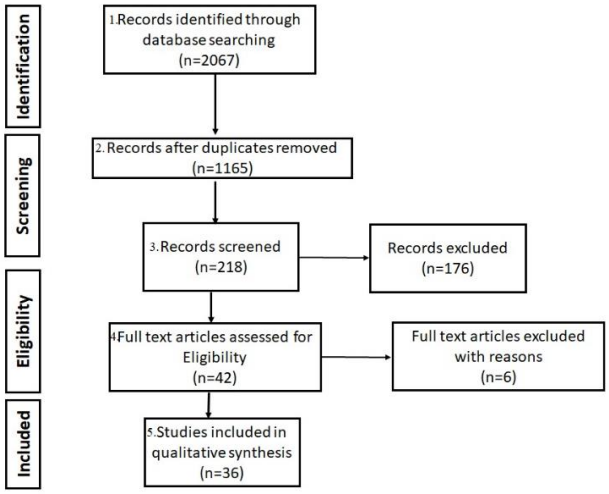

Figure 1. PRISMA flowchart of the literature search and strategy for the selection of relevant document.

Systematic review findings.

In the present review, studies were conducted in South Korea (8 articles), Turkey and Spain (3 articles in each country), China, Portugal, France, Italy (2 articles in each country), Czech Republic, Canada, Austria, England, Taiwan, Greece, USA, Japan, Croatia, Romania, Tunisia, Tunisia, Hungary, Netherland (1 article in each country). Totally 8584 patients were evaluated in 37 included studies. These studies were conducted on 8584 adults who were 4048 men and 4536 women aged 25–55. Patients mostly suffered from IBD, RA, AS, PsA and psoriasis and UCTD, respectively. The thirty-seven articles were selected for systematic review study were diagnostic test studies. Two studies had a retrospective case-control, eighteen studies had a prospective cohort design, three studies had a retrospective cohort and twelve studies had a cohort design. One study was cross-sectional and one study had a prospective cross sectional design and three studies had case-control design. The twenty- three articles were from countries with low TB prevalence and 14 articles were from countries with high TB prevalence. Articles conducted by Slouma (2017), Lee (2015), Kim (2014), Jung (2014), Lopez (2013), Constsntino (2013), Singanayagam (2013), Sauzullo (2013), Andrisani (2013), Greveson (2013), Saidenberg-kermana (2012), Ramos (2012), Hatemi (2012), Vassilopoulos (2011), Ringrose (2011), Inanc (2009), Shovman, Jung (2012), Sellami (2018), He (2013) and Chang (2010) indicated 96%, 69%, 70.70%, 79.80%, 88.90%, 78%, 34.8%, 22.3%, 1.10%, 87%, 56.10%, 29%, 24%, 76%, 41.60%, RA:77% AS:95%, 74%, 76.30%, 88.5%, 78.20% and 60% of patients received BCG vaccination, respectively. The twenty-five studies evaluated the effect of glucocorticoid on false-positive results of TST. TNF-α inhibitors were mostly used including infliximab, adalimumab, etanercept, golimumab and certolizumab in these studies, respectively (**Table 1**).

Studies comparing TST and QFT-GT and evaluating the clinical outcome of LTBI in patients under anti-TNF-α inhibitor therapy.

Takahashi and co-workers (2007) studied the effectiveness of TST and QFT-GT bimonthly in 14 RA patients under TNF-α inhibitor therapy for diagnosing LTBI. These tests indicated 7 patients with LTBI positive. Among them, the positive results of QFT-GT in 4

patients caused during TNF-α inhibitor treatment that two of them was detected only by QFT-GT. The agreement rate between TST and QFT-GT was 64.3%. The study suggested the use of two studies for LTBI in RA patients [10]. The study conducted by Park et al., (2009) focused on the TST and QFT-GT assays for detecting LTBI in Korean patients (RA, AS, JRA patients) with initial negative TST under TNF-α blocker treatment for over one year. Duration TNF-α blocker treatment, some TST results non-significantly converted to positive. Nine of patients under QFT-GT indicated positive results. 22 patients with TST positive suffered from RA. The concordance between TST and QFT-GT was 68.6%. The study indicated TST with QFT-GT may be useful to identify false-results during long term TNF-α inhibitors treatment, particularly in a country with a middle TB prevalence [11]. Papay et al., (2012) evaluated QFT-GT and TST in IBD patients under TNF-α antagonist therapy for 5 months for detecting LTBI. Then, QFT-GT and TST were retested. In subjects without LTBI positive at baseline, QFT-GT was not converted to positive, but 4.2% of TST negative results converted to positive. TNF-α blocker treatment caused conversion of TST. As compared with TST, the results of QFT-GT assay reverted in 50% of patients under isoniazid-treated for LTBI. However, patients with QFT-GT positive results could not develop active TB [12]. Chen et al., (2012) evaluated the QFT-GT and TST for diagnosing TB in 242 RA patients under TNFα blocker treatment for a long time. Among 242 RA patients, seventy five indicated TST positive and forty five indicated QFT-GT positive results, and 9 of them indicating indeterminate QFT-GT assay. 37 patients showing TST positive and 24 patients showing TST positive and QFT-GT negative treated with isoniazid. After 3 months of TNF-α blocker therapy, 4 patients had active TB, whereas 5 patients with baseline TST and QFT-GT negative results developed active TB. QFT-GT conversion was seen in patients with QFT-GT negative results who had active TB underwent anti-TNF-α treatment [13]. Andrisani et al., (2013) investigated QFT-GT and TST assays for detecting LTBI in IBD patients with negative TB under TNF-α blocker therapy. The agreement between two tests was modest in the patients, while it was very low in subjects under TNF-α blocker therapy. The study suggested that anti-TNF-α therapy may activate LTBI and two tests were useful in patients with low TB and BCG vaccination rates, [14]. Case-control study designed by Inanc and co-workers (2015) assessed the QTF-G and TST for detecting LTBI in 140 patients with RA and AS following 6 months of TNF- inhibitor therapy. The rate of positive results of QTF-GT was similar in RA, AS and healthy control. A great percentage of positive TST was seen in AS patients. The concordance between QTF-G and TST was 61% in the whole group, 70% in RA, and 49% in AS. TNF-α antagonists therapy changed a great percentage of indeterminate results of QTF-GT to positive [15]. Ramos et al., (2015) evaluated the efficiency of QFT-GT and TST for diagnosing LTBI in 115 patients under TNF-α blocker therapy. 52 patients had LTBI at baseline that 50 of them were selected for TB treatment. No active TB was seen in patients with LTBI positive at baseline. Under anti-TNF-α, active TB developed in 2 of the patients with negative results. TST conversion was observed in 5 cases. No QFT-GT conversions were seen. The concordance between TST and QFT-GT is poor. QFT-GT acted more effective for diagnosis LTBI in patients under TNF-α blocker therapy [16]. Lee et al., (2018) evaluated TST and QFT-GT for diagnosis LTBI in 108 patients (83 IBD; 25 RA diseases) under TNF-α blocker therapy. At baseline, 18 patients had positive LTBI that 14 of them treated with isoniazid for 9 months. Anti-TNF-α therapy changed LTBI test results of 17 patients and 14 subjects of them treated with isoniazid. The study indicated that TNF-α inhibitor therapy had no effect on LTBI test conversion. LTBI in a CD patient changed to active TB after 20 months of infliximab therapy. LTBI was not diagnosed at first evaluation. Infliximab converted IGRA after four months. He was under isoniazid therapy nine months for LTBI treatment. After 7 months, he admitted with fever and cough and also whitish sputum. Patients with LTBI conversion and high QFT-G levels may have a great risk of progression of active TB and they need follow-up for several months. [17]. Slouma et al., (2017) assessed the efficacy of TST and QFT-GT for diagnosis LTBI in patients with chronic inflammatory rheumatism (70.8% RA) under TNF-α blocker treatment for at least 6 months. LTBI was seen in 23 patients. Among them, 12 patients had negative TST and positive QFT-GT. In patients with positive LTBI, TB was treated before TNF-α blocker therapy. Active TB has not occurred in patients with positive LTBI. Two subjects with active TB were observed in patients with negative results of TST and QFT-GT The study suggested that LTBI screening and a prophylactic treatment support the safety of biological therapy [18]. Soare et al., (2018) assessed the efficacy of TST and QFT-GT for predicting active TB in RA, PsA and AS receiving TNF-α blocker therapy. The proportion of patients with positive LTBI was similar to TST2 (TST with positive threshold= 10 mm) and QFT. However, TST1 ((TST with positive threshold= 5 mm)) detected fewer patients with positive LTBI than TST2. During the first year of TNF-α blocker treatment, active TB occurred in 3/8, 1/9 and 1/3 of positive LTBI patients that detected by assays, respectively. However, fewer TB subjects were enrolled in the QFT group, likely due to the decreased duration of time exposure to TNF-α. No marked risk factors for progressing active TB. In the study, observed TB after 1 year of TNF-α inhibitor therapy, indicating the importance of more and exact screening tests for diagnosing LTBI [19].

Studies comparing TST and QFT-GIT and evaluating the clinical outcome of LTBI in patients under anti-TNF-α inhibitor therapy.

Ringrose et al., (2011) evaluated patients for diagnosing LTBI before anti-TNF-α therapy by using TST and QFT-GIT assays and chest x-ray (CXR). Patients with a TST or QFT-GIT positive results were evaluated at 3 and 6 months after anti-TNF-α therapy. Among 106 patients, 26 patients had a positive TST or QFT-GIT at baseline; 12 of them treated with anti-TNF-α for 6-month. The TST for the 12 subjects was 13.9 mm that increased to 16.8 mm post-booster. After 3 months of anti-TNF-α therapy, TST decreased below 5 mm in 3 of the 12 patients. The QFT-GIT was not converted during the study period in patients. The concordance between TST and QFT-GIT was weak. A marked reduction in TST response was observed in the first six months of anti-TNF-α treatment [20]. Qumseya et al., 2011 evaluated the efficiency of the QFT-GIT for diagnosing LTBI in 340 IBD patients in the

United States. Five patients had a positive QFT-GIT, nine patients were indeterminate, and 326 patients had a negative QFT-GIT. After 17 months, one case of them had active TB. TNF-α inhibitors did not affect the QFT-GIT results. Agreement between the TST and QFT-GIT was moderate. TNF-α inhibitors mostly did not change negative QFT-GIT results and could not activated TB. TNF-α inhibitors developed TB in one patient with indeterminate QFT-GIT [21].

Chang et al., (2011) evaluate the usefulness of the IGRAs for diagnosing LTBI in RA and AS patients under TNF-α blocker therapy in Korea by TST, QFT-GIT, and chest radiography. 36 patients with positive QFT-IGT result was treated for LTBI. For one patient with indeterminate QFT-GIT results, TST positive result was considered for LTBI treatment. No patients developed TB during a median of 18 months of TNF blocker therapy. Sixteen patients with positive TST and negative QFT-GIT results, TNF blockers were administrated without LTBI treatment. Tuberculosis was not observed in these patients, during TNF inhibitors therapy. The study suggested QFT-GIT may be better than TST for diagnosing LTBI in patients before TNF inhibitors therapy in countries with middle burden of tuberculosis and BCG vaccination at birth [22]. Saidenberg-Kermanac'h et al., 2012 also screened for LTBI in 123 patients with IRDs under anti-TNF-α by using chest X-ray and TST (protocol 1) and also chest X-ray and TST plus QFT-GIT (protocol 2) in France. LTBI was diagnosed in 59 patients with protocol 1 and 69 LTBI cases by protocol 2. TB was diagnosed in 3 RA patients with negative tests. Although, the study indicated that the accuracy of QFT-GIT was higher than TST, two tests should be done for diagnosing LTBI in patients with IRD in countries with a high prevalence of TB [23]. Hatemi et al., (2012) screened LTBI in RA patients under TNF-α antagonists therapy and healthy subjects by TST and QFT-GIT. Treatment with TNF-α antagonists did not change the QTF-GIT and TST positive results [24]. Ramos et al., (2013) used the TST and QFT-GIT for diagnosing LTBI in RA, PS, IBD and SA among patients with and without TNF-α antagonists therapy. A significant difference was observed in the percentage of positive QFT-GIT among patients with and without TNF-α antagonists therapy after adjustment for age and gender. Concordance between TST and QFG-GIT was poor in patients under TNF-α antagonists therapy and was moderate in patients without TNF-α antagonists therapy. The study suggested that TNF-α antagonists therapy had negative effect on the performance of QFT-GIT [25]. Sauzullo et al., 2013 evaluated the interferon (IFN)-c response to mycobacterium tuberculosis-specific antigens by using TST and serial QFT-GIT assay in patients with psoriasis under long-term TNF-α inhibitors therapy. IFN-c release may occur in patients with psoriasis under TNF-α antagonists therapy. The changes of IFN-c levels might be suitable for diagnosing LTBI reactivation in patients under anti-TNF-α treatment [26]. Klein et al., (2013) screened for LTBI during and prior to TNF-α inhibitors treatment in patients with several rheumatic inflammatory diseases by using TST and QFT-GIT. QFT-GIT positive was seen in 22 patients before and during TNF-α inhibitor therapy treatment (3.9 and 5.9%, respectively). TB activated in 2 patients with QFT-GIT positive. TST positive was observed in patients before and during treatment (42% and 38%, respectively). Agreement between TST and QFT-GIT was poor. Poor association between the TST and QFT-GIT exhibits that TST is non-specific test for diagnosing LTBI and QFT-GIT is more specific [27]. Lee et al., (2013) screened LTBI in RA and AS patients with TNF-α inhibitors therapy by TST and QFT-GIT. TB developed in 9 patients. They indicated that TB increased in patients under TNF-α inhibitors therapy. The study suggested that additional assays are needed for diagnosing TB in patients with long-term therapy with TNF-α inhibitors therapy [28]. Bermejo et al., 2013 compared the performance of TST and QFT-GIT in IBD patients with TNF-α inhibitors therapy. After TNF-α inhibitors therapy, 4 patients were detected with potential TB. The TST conversion rate was 0.83% per patient-year of treatment with anti-TNF drugs. QFT-GIT with indeterminate and negative results were observed for 2 patients. The conversion rate of TST in patients with TNF-α therapy was low and these conversions were detected according to a positive TST and were not similar to QFT-GIT [29]. Kim et al., (2014) compared TST and QFT-GIT assay for detecting LTBI in patients with TNF-α inhibitors therapy. The prevalence rates of positive TST and QFT-GIT were 22.3% and 16.0%, respectively. LTBI was treated in 25.1% of patients. During follow-up, active TB was seen in 1.4% of the patients with negative TST and QFT-GIT results at baseline. The findings suggested that TST and QFT-GIT are useful for detecting LTBI prior to TNF-α blocker therapy in patients [30]. Lee et al., (2015) assessed the performance of the QFT-GIT and TST for diagnosing LTBI in RA and AS patients with TNF-α inhibitors treatment. LTBI treatment was done according to the positive QFT-GIT results. TST and QFT-GIT positive results were observed in 35.7% and 30.1% of patients. After 20.8 months of TNF-α inhibitors treatment, TB developed in 1.5% patients. TB was not observed in TST+/QFT+ patients who treated for LTBI. Active TB was observed in 2.5% of patients with TST−/QFT+ who treated for LTBI, 3.3 of patients with TST+/QFT− who did not treat for LTBI after TNF-α inhibitors treatment (705/100,000person-years).Among patients who did not treated for LTBI, active TB was seen in 3.3% months after 7.2 months of TNF-α inhibitors treatment. Active TB was observed in 1.1% of patients after 22.7 months of TNF-α inhibitors treatment. The incidence rate of TB was similar between TST+/QFT−, TST−/QFT+ and TST−/QFT− patients. QFT-GIT might be useful for detecting LTBI in patients prior to TNF-α inhibitors treatment in population with middle prevalence of TB and BCG vaccination at birth [31]. Kurti et al., 2015 compared the concordance of TST with QFT-GIT in 166 BCG-vaccinated IBD patients treated with TNF-α inhibitors. The positive rate of TST was 23.5%, 21.1%, 14.5% and 13.9% with cut-off values of 5, 10, 15 and 20 mm. The positive rate of QFT-GIT was 8.4% and indeterminate result rate was 0.6%. Chest X-ray detected 2 patients with LTBI. Agreement between QFT-GIT and TST and was moderate. TNF-α inhibitors had no effect on the positive rate of TST and QFT-GIT [32]. Çekiç et al., (2015) indicated the percentage of active TB in IBD patients under TNF-α inhibitors by using TST and QFT-GIT. LTBI was detected and treated in 59.2% patients. Active TB was seen in 4.7% patients who did not treat for LTBI. Agreement between TST and QFT-GIT was moderate. TNF-α inhibitors did not change TST results [33]. Baričević1 et al., (2017) compared the performance QFT-GIT and TST for diagnosing LTBI in RA, CD, AS and PA patients prior to TNF-α inhibitors therapy. The positive QFT-GIT results were treated for LTBI. The high

agreement was observed between QFT-GIT and TST results. Positive QFT-GIT test converted to negative in 4% of patients, while QFT negative was not changed [34].

Table 1. Characteristic of selected studies

First author & Publication year	Country	Number Of patients	Type of disease	Mean age (year)	Female (%)	BCG vaccinated (%)	IGRA used	TST cut off (mm)
He.D (2013)	Shanghai	101	RA/AS/PsA	47	71.2	78.2	T-Spot.TB	10
Lee.C.K (2018)	Hongkong	108	IMD/RA/AS/ PsA	36.5	37.9	-	QFT-GT	5
Aberu .C (2017)	Portugal	46	IBD	36.7±12	60		QFT-GIT T-SPOT.TB	
Slouma.M (2017)	Tunesia	113	IBD/RA AS/PsA/other	47.76±13.5	96.02	97.3	QFT-GT	10
Kurti.Z (2015)	Hungary	16	IBD	24	48.1		QFT-GT	5
Ramos.S (2015)	Portugd	115	IBD/RA/AS/ PsA/other	41±11.S	47.8		QFT-GT	5
Kim.E.S (2015)	S.Korea	376	IBD	32.S±13	32.1		QFT-GT	
Lee.H (2015)	S.Korea	342	IBD/RA/AS	40	44.4	69	QFT-GT	
Kim.H.C (2014)	S.Korea	456	IBD/RA/AS	41.1±15.8	43.8	70.6	QFT-GIT	10
Jung.Y.J (2014)	S.Korea	430	IBD/RA/AS/ other	39.9±16	48.1	79.7	T-Spot.TB	10
Kim.J.H(2014)	S.Korea	842	RA/AS/PsA/J RA	44.5±14.9	56		QFT-GIT	5
Constantino.F (2014)	France	563	RA/AS	SI	27.1	87.5	T-Spot.TB	5
Jo.K.W (2013)	S.Korea	101	IBD/AR/AS/ PsA	40.4±16	49.5		QFT-GIT T-SPOT.TB	10
Singanayagam.A (2013)	London	187	RA/AS/PsA/o ther	54	56.1	34.7	QFT-GIT T-SPOT.TB	BCG+:15 BCG-:6
Sauzullo.I (2013)	Italy	148	Psoriasis, PsA	49	65.5	22.2	QFT-GIT	BCG+ :10 BCG-:5
Bermejo.F (2013)	Spain	74	IBD	42±B	55.4	0.06		
Andrisani.G (2013)	Italy	92	IBD	39.6	50	1.08	QFT-GT	5
Klein.M (2013)	Czech Republic	3.5	RA/AS/PsA/ other	44.18±14.77	54.09		QFT-GT	5
Pappy.P (2012)	Austria	227	IBD	36.1±10.6	51.9		QFT-GT	S
Saidenberg-Kermanac'h.N (2012)	France	128	RA/AS/PsA/ other	50.4±11.9		56.09	QFT-GT	S
Ramos J.M (2012)	Spain	123	IBD/RA/AS/ PsA /other	52		18.9	QFT-GT	S
Hatemi.G (2012)	Turkey	76		51.7±14.7		31.5	QFT-GT	10
Minguez.S (2012)	Spain	23	RA/AS/PsA/ other				QFT-GIT/T-SPOT.TB	S
Chen.D.J(2012)	Taiwan	233	RA	24.7±B.66		63	QFT-GT	S
Vassilopoulos.D (2011)	Creece	122	RA/AS/PsA /Other	27±16		66.4	QFT-GIT/ T-SPOT.TB	S
Ringrose.T.S (2011)	Canada	12	RA/AS/PsA	55.7	58.3	41.6	QFT-GIT	10
Qumseya.B (2011)	Us	340	IBD	41±15	54.4		QFT-GT	5
Inanc.N (2009)	Turkey	140	RA/AS	45	67.8	84.2	QFT-GT	5
Park.J.H (2009)	S.Korea	86	RA/AS/other	39.2±15.8	55.8	89.5	QFT-GIT	10
Takahashi.H (2009)	Japan	14	RA	48.6	78.5		QFT-GT	
Lee.S.K (2013)	S.Korea	509	IBD/RA/AS/ PsA/other	43	52.6		QFT-GT	
Jung.y.J (2012)	S.Korea	281	IBD/RA/AS/o ther	40.1±14.7	39.1	76.2	QFT-GIT/ T-SPOT.TB	10
Baricevic.D (2017)	Croatia	300		48.48	52.3			10
Soare.A (2018)	Romania	550	RA/AS/PsA	55.1±14.1	54.3			
Cekic.C (2015)	Turkey	76	IBD	42±12.4	30.2		QFT-GIT	5
Chang.B (2011)		110	RA/AS/other		43.6	54.5	QFT-GIT	

Studies comparing TST and both QFT and T-SPOT.TB or T-SPOT.TB and evaluating the clinical outcome of LTBI in patients under anti-TNF-α inhibitor therapy.

Jo et al., 2013 investigated the results of anti-TNF-α therapy in CD, RA and AS patients with a history of TB under anti-TNF-α therapy by using QFT-GIT and TSPOT. Chest radiography indicated TB lesions in 32.7% patients. The positive rates of TST and IGRAS were 21.8% and 44.6%, respectively. 10.9% of patients treated for LTBI. Active TB was observed in 1% of patient without LTBI treatment six years after the TNF-α antagonist therapy. Patients with history of TB and under TNF-α inhibitors had an acceptable rate of TB if treated for LTBI [35].

Abreu et al. (2017) screened LTBI by TST and two different IGRAs assays [QFT-GIT and T-SPOT.TB] in IBD patients under anti-TNF-α therapy for 26 months. LTBI were detecting in 16 patients: TST positive in 12 patients; T-SPOT positive in 7 patients, QFT-GIT positive in 2 patients. LTBI treated for 15 patients. TST have higher sensitivity than the IGRAs according to interferon ϒ release [36]. Kim ES et al. (2015) investigated LTBI in IBD patients under TNF-α inhibitors therapy using TST, QFT-GIT and TSPOT prior to treatment. LTBI was diagnosed in 8% of patients. Active TB occurred in 16 cases after TNF-α inhibitors therapy. The study indicated that TNF-α inhibitors increased the risk of TB in IBD patients [37]. Mínguez et al. (2012) screened LTBI in RA patients under TNF-α inhibitors therapy by using TST, QFN-G-IT, and T-SPOT.TB. TST, T-SPOT.TB and QFN-GIT positive were seen in 7, 11 and 9 cases, respectively. Agreement between TST and T-SPOT.TB was 77.35% and TST and QFN-G-IT were 83.01%. TNF-α inhibitors had no effect on positive TST, T-SPOT.TB and QFN-GIT results. The study suggested that both TST and IGRAs should be done for diagnosing LTBI in patients with a high risk of developing active TB [38]. Vassilopoulos et al. (2011) compared the performances of TST, T-SPOT.TB and QFT-GIT for detecting LTBI screening in RA patients under TNF-α inhibitors therapies. The concordance between IGRAs was 81% that was higher than agreement TST and IGRAs. IGRAs seemed better TB than TST and should be considered for diagnosing TB in patients under TNF-α inhibitors treatment [39]. Costantino et al., (2014) assessed LTBI in RA and SA patients under TNF-α inhibitors treatment by TST and IGRAs. Concordance between TST and IGRAs was poor. The positive rate of TST was 34.8%. T-SPOT.TB positive percentage was in 21.7% and indeterminate percentage was 15.6%. Previous active TB and chest radiograph abnormalities were related to IGRA positive results. The study suggested that the usefulness of combined T-SPOT.TB and TST in patients prior to TNF-α inhibitors treatment [40]. He et al. (2013) screened for LTBI in RA patients and healthy subjects under TNF-α inhibitors therapy by using IGRAs and TST. The positive rates of TST were 37.6% in patients and 34.0% in healthy subjects, while the positive rates of T-SPOT.TB was 46.5% in patients and 21.1% in healthy cases. Biological therapy converted T-SPOT. TB positive results, conversion rate was 11.2%. Active TB was not observed in T-SPOT. TB screening results. It was suggested that biologics therapy increased the risk of TB [41]. Jung et al. (2012) evaluated LTBI in patients with anti-TNF therapy by using TST and T-SPOT. Positive percentage for TST and T-SPOT were 33.6% and 69.1%, respectively. 35.9% of the patients were treated for LTBI and active TB was seen in 2.1% patients. Among active TB patients, TST negative was observed in 50% of patients and did treated for LTBI, whereas 60% of them had T-SPOT positive results at baseline. It was indicated that TST had limitation for diagnosing LTBI in population with TB prevalence, TST-defined LTBI diagnosis and treatment seem to be limited in preventing the development of TB before anti-TNF treatment [42]. Singanayagam et al., (2013) screened LTBI in RA patients prior to anti-TNF-α therapy. 80.3% of patients were considered as low risk for LTBI. 35.5% of patients with TST and T.SPOT positive were low risk. The study suggested the combination of TST and T.SPOT act potentially for diagnosing LTBI compared alone [43]. In a study conducted by Jung et al., (2014) evaluated LTBI in patients under TNF-α inhibitors treatment by using TST and T-SPOT. Positive TST and T-SPOT result was considered as LTBI. The positive rates for the T-SPOT assay and TST were 19.1% and 44.2%, respectively. 46.0% of patients were treated for LTBI. Active TB was observed in 0.9% of the patients. Both TST and T-SPOT assays are useful for diagnosing LTBI prior to the TNF-α inhibitors treatment in population with TB prevalence [44].

Discussion.

No suitable a gold standard for detection LTBI, assessment of the efficacy of TST and IGRAs continues. Particularly for patients with chronic inflammatory disorders prior to biologic therapy, is necessary to detect LTBI for preventing active TB. This study is an updated systematic study for evaluating the efficiency of IGRA and TST assays for diagnosis LTBI in patients under TNF-α blocker therapy. Tuberculosis diagnosis assays are necessary for patients with chronic inflammatory disorders before TNF-α antagonist therapy, due to a decrease in the risk of LTBI activation. TST and QFT-GT are the common assays used for detection LTBI. Numerous studies have evaluated the efficiency of TST and QFT for detecting LTBI, but only a few numbers of them have assessed these two tests in patients under anti-TNF-α therapy. The present study found that the agreement between QFT-GT and TST results is poor to moderate and TNF-α blocker therapy mostly decreased the percentage of this agreement. Although present findings have several limitations including the small number of subjects in selected studied, it might be suggested in country with low TB prevalence and low BCG vaccination rate, both tests are useful. However, the findings of patients under TNF-α inhibitors therapy suggest the difference between TST and QFT results. Active TB was mostly seen in patients with negative TST and QFT-GT. Anti-TNF-α therapy could mostly develop active TB in patients with negative LTBI results. TST conversion under anti-TNF-α therapy was more observed in some cases than QFT-GT conversion. The present study found that TST with QFT-GT may be effective in diagnosis false-results during long term TNF-α inhibitor treatment, particularly in population with intermediate TB prevalence. According to the present findings, the concordance between TST and QFT-GIT is also poor to moderate. TNF-α antagonists treatment had no significant impact on the QTF-GIT results. Although, QFT-GIT had higher diagnostic accuracy than TST and may be used instead of TST for the detection of LTBI in patients prior to TNF inhibitors in population with intermediate prevalence of TB, only one test was not able to diagnosis all patients at high risk for active TB. We reviewed 37 studies to compare the performance of IGRAs versus TST in patients under TNF-α blocker therapy. We found that the association between IGRAs and TST was poor to moderate. Additionally, the association between TST and T-SPOT.TB was higher than TST and QFT-GIT. The development of active TB in patients under TNF-α antagonists might be main outcome to evaluate the efficacy of assay. However, only seventeen of our included studies [25, 27, 33, 36] reported the follow-up data of patient and 74 active cases were reported [36]. The concordance between IGRAs and TST was poor to moderate which demonstrates the differences between these two tests. TST results were markedly related to BCG vaccination in subjects. However, BCG vaccination was not a confounding factor for IGRAs. False-

positive TST may lead to un-necessary tuberculosis therapy. Indeterminate results of IGRAs may be associated with the negative control tests positive regardless of the response to TB-specific antigens or (2) the positive control tests negative as does the response to TB specific antigens. Actually, most indeterminate results in immunocompromised patients resulted from the negative response against mitogen which was used as positive control [35]. Altogether, IGRA is mostly preferred in selected articles, but, the high expense of IGRAs has decreased its application in patients under TNF-α inhibitors therapy. According to the present findings, in patients with BCG vaccination history, IGRAs might be better for diagnosis LTBI than TST due to its low false results. The negative data, especially negative TST should be interpreted with caution in patients treated with any steroid. Additional data such as history of TB, chest radiograph, and other risk factors of TB is necessary if the test results are negative. Limitations of present study: First, we could not evaluate the efficacy of IGRAs to prevent the development of active TB due to no enough data. Second, the met analysis study is needed to compare exactly the efficacy of IGRAs and TST.

4. CONCLUSIONS

In the treated patients with anti-TNF-α with previous BCG vaccination, IGRAs might be the better assay to diagnosis LTBI by reducing the false results rate in comparison with the TST. However, more investigations should be done to compare the advantage of IGRAs with conventional test in the treated patients with TNF-α antagonists.

5. REFERENCES

1. Modi, A.R.; Miranda, C.C.; Procop, G.W.; Foster, C.B.; Harrington, S.; Evans, D.; Johnson, L.T.; Gordon, S.M. Addressing the threat from within Investigation of respiratory symptoms in a health care worker with untreated latent tuberculosis infection. *Am J Infect Control.* **2019**, *S0196-6553*, 30692-3, https://doi.org/10.1016/j.ajic.2019.07.012.
2. Overton, K.; Varma, R.; Post, J.J. Comparison of Interferon-γ Release Assays and the Tuberculin Skin Test for Diagnosis of Tuberculosis in Human Immunodeficiency Virus: A Systematic Review. *Tuberc Respir Dis (Seoul).* **2018**, *81*, 59-72, https://doi.org/10.4046/trd.2017.0072.
3. Clunie, G.; McInnes, I.B.; Barkham, N.; Marzo-Ortega, H.; Patel, Y.; Gough, A.; Packham, J.; Kyle, S.; Kirkham, B.; Sheeran, T.; Coope. H.; Bishop-Bailey, A.; McHugh, N. Long-term effectiveness of tumour necrosis factor-α inhibitor treatment for psoriatic arthritis in the UK: a multicentre retrospective study. *Rheumatol Adv Pract.* **2018**, *2*, rky042, https://doi.org/10.1093/rap%2Frky042.
4. Zhang, Z.; Fan, W.; Yang, G.; Xu, Z.; Wang, J.; Cheng, Q.; Yu, M. Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* **2017**, *7*, e012567, https://doi.org/10.1136/bmjopen-2016-012567.
5. Bonvicini, F.; Cilloni, S.; Fornaciari, R.; Casoni, C.; Marchesi, C.; Greci, M.; Monici, L.; Nicolini, F.; Vinceti, M. Compliance with Tuberculosis Screening in Irregular Immigrants. *Int J Environ Res Public Health*. **2018**, *16*, E28, https://doi.org/10.3390/ijerph16010028.
6. Boskovska, K.; Naceva-Fustic, S.; Simonovska, L.; Dilberovska, M.; Dacevski, D.; Popova, G.; Arnaudova, I.; Cakalarovska, I. Comparison of IFN-γ Levels in Children with Tuberculosis Disease (TB) and Latent Tuberculosis Infection (LTBI). *Open Access Maced J Med Sci.* **2018**, *6*, 2091-2096.
7. Meier, N.R.; Jacobsen, M.; Ottenhoff, T.H.M.; Ritz, N. A Systematic Review on Novel Mycobacterium tuberculosis Antigens and Their Discriminatory Potential for the Diagnosis of Latent and Active Tuberculosis. *Front Immunol.* **2018**, *9*,2476, https://doi.org/10.3389/fimmu.2018.02476.
8. González-Moreno, J.; García-Gasalla, M.; Losada-López, I.; Cifuentes, L.C.; Mir, V.I.; Fernández-Baca, V.; Serrano, A.; Juan, M.A.; Riera-Oliver, J.; Payeras, C.A. IGRA testing in patients with immune-mediated inflammatory diseases: which factors influence the results? *Rheumatol Int.* **2018**, *38*, 267-273, https://doi.org/10.1007/s00296-017-3852-9.
9. Sargın, G.; Şentürk, T.; Ceylan, E.; Telli, M.; Çildağ, S.; Doğan, H. TST, QuantiFERON-TB Gold test and T-SPOT.TB test for detecting latent tuberculosis infection in patients with rheumatic disease prior to anti-TNF therapy. *Tuberk Toraks*. **2018,** *66*, 136-143, https://doi.org/10.5578/tt.66444.
10. Takahashi, H.; Shigehara, K.; Yamamoto, M.; Suzuki, C.; Naishiro, Y.; Tamura, Y.; Hirohashi, Y.; Satoh, N.; Shijubo, N.; Shinomura, Y.; Imai, K. Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. *Rheumatol Int.* **2007**, *27*, 1143-8, https://doi.org/10.1007/s00296-007-0361-2.
11. Park, J.H.; Seo, G.Y.; Lee, J.S.; Kim, T.H.; Yoo, D.H. Positive conversion of tuberculin skin test and performance of interferon release assay to detect hidden tuberculosis infection during anti-tumor necrosis factor agent trial. *J Rheumatol*. **2009**, *36*, 2158-63, https://doi.org/10.3899/jrheum.090150.
12. Papay, P.; Primas, C.; Eser, A.; Novacek, G.; Winkler, S.; Frantal, S.; Angelberger, S.; Mikulits, A.; Dejaco, C.; Kazemi-Shirazi, L.; Vogelsang, H.; Reinisch, W. Retesting for latent tuberculosis in patients with inflammatory bowel disease treated with TNF-α inhibitors. *Aliment Pharmacol Ther*. **2012**, *36*, 858-65, https://doi.org/10.1111/apt.12037.
13. Chen, D.Y.; Shen, G.H.; Chen, Y.M.; Chen, H.H.; Hsieh, C.W.; Lan, J.L. Biphasic emergence of active tuberculosis in rheumatoid arthritis patients receiving TNFα inhibitors: the utility of IFNγ assay. *Ann Rheum Dis*. **2012**, *71*, 231-7, https://doi.org/10.1136/annrheumdis-2011-200489.
14. Andrisani, G.; Armuzzi, A.; Papa, A.; Marzo, M.; Felice, C.; Pugliese, D.; De Vitis, I.; Rapaccini, G.L.; Guidi, L. Comparison of Quantiferon-TB Gold versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease patients. *J Gastrointestin Liver Dis*. **2013**, *22*, 21-5.
15. Inanc, N.; Aydin, S.Z.; Karakurt, S.; Atagunduz, P.; Yavuz, S.; Direskeneli, H. Agreement between Quantiferon-TB gold test and tuberculin skin test in the identification of latent tuberculosis infection in patients with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol.* **2009**, *36*, 2675-81, https://doi.org/10.3899/jrheum.090268.
16. Ramos, S.; Nogueira, A.; Dias, A.; Gonçalves, A.F.; Gaio, A.R.; Duarte, R. Tuberculosis screening in patients receiving biological therapy. *Acta Reumatol Port.* **2015**, *40*, 234-40.
17. Lee, C.K.; Wong, S.H.V.; Lui, G.; Tang, W.; Tam, L.S.; Ip, M.; Hung, E.; Chen, M.; Wu, J.C.; Ng, S.C. A Prospective Study to Monitor for Tuberculosis During Anti-tumour Necrosis Factor Therapy in Patients With Inflammatory Bowel Disease and Immune-mediated Inflammatory Diseases. *J Crohns Colitis* **2018**, *12*, 954-962, https://doi.org/10.1093/ecco-jcc/jjy057.

18. Slouma. M.; Mahmoud, I.; Saidane, O.; Bouden, S.; Abdelmoula, L. Latent tuberculosis infection screening prior to biological treatment in Tunisian patients. *Therapie* **2017,** *72*, 573-578, https://doi.org/10.1016/j.therap.2017.02.002.
19. Soare, A.; Gheorghiu, A.M.; Aramă, V.; Bumbăcea, D.; Dobrotă, R.; Oneaţă, R.; Pintilie, S.; Milicescu, M.; Ancuţa, I.; Martin, A.; Sasu, M.; Ciofu, C.; Macovei, L.; Stoica, V.; Bojincă, M.; Mihai, C. Risk of active tuberculosis in patients with inflammatory arthritis receiving TNF inhibitors: a look beyond the baseline tuberculosis screening protocol. *Clin Rheumatol.* **2018**, *37*, 2391-2397, https://doi.org/10.1007/s10067-017-3916-y.
20. Ringrose, J.S.; Sanche, S.E.; Taylor-Gjevre, R.M. Detecting latent tuberculosis infection during anti-tumour necrosis factor therapy. *Clin Exp Rheumatol*. **2011**, *29*, 790-4.
21. Qumseya, B.J.; Ananthakrishnan, A.N.; Skaros, S.; Bonner, M.; Issa, M.; Zadvornova, Y.; Naik, A.; Perera, L.; Binion, D.G. QuantiFERON TB gold testing for tuberculosis screening in an inflammatory bowel disease cohort in the United States. *Inflamm Bowel Dis.* **2011**, *17*, 77-83, https://doi.org/10.1002/ibd.21329.
22. Chang, B.; Park, H.Y.; Jeon, K.; Ahn, J.K.; Cha, H.S.; Koh, E.M.; Kang, E.S.; Koh, W.J. Interferon-γ release assay in the diagnosis of latent tuberculosis infection in arthritis patients treated with tumor necrosis factor antagonists in Korea. *Clin Rheumatol*. **2011,** *30*, 1535-41, https://doi.org/10.1007/s10067-011-1771-9.
23. Saidenberg-Kermanac'h, N.; Semerano, L.; Naccache, J.M.; Brauner, M.; Falgarone, G.; Dumont-Fischer, D.; Guillot, X.; Valeyre, D.; Boissier, M.C. Screening for latent tuberculosis in anti-TNF-α candidate patients in a high tuberculosis incidence setting. *Int J Tuberc Lung Dis.* **2012**, 16, 1307-14, https://doi.org/10.5588/ijtld.12.0111.
24. Hatemi, G.; Melikoglu, M.; Ozbakir, F.; Tascilar, K.; Yazici, H. Quantiferon-TB Gold in tube assay for the screening of tuberculosis before and during treatment with tumor necrosis factor alpha antagonists. *Arthritis Res Ther.* **2012**, *14*, R147, https://doi.org/10.1186/ar3882.
25. Ramos, J.M.; Masiá, M.; Rodríguez, J.C.; López, C.; Padilla, S.; Robledano, C.; Navarro-Blasco, F.J.; Matarredona, J.; García-Sepulcre, M.F.; Gutiérrez, F. Negative effect of immunosuppressive therapy in the performance of the QuantiFERON gold in-tube test in patients with immune-mediated inflammatory diseases. *Clin Exp Med.* **2013**, *13*, 177-86, https://doi.org/10.1007/s10238-012-0192-7.
26. Sauzullo, I.; Mengoni, F.; Marocco, R.; Potenza, C.; Skroza, N.; Tieghi, T.; Lichtner, M.; Vullo, V.; Mastroianni, C.M. Interferon-c release assay for tuberculosis in patients with psoriasis treated with tumour necrosis factor antagonists: in vivo and in vitro analysis. *Br J Dermatol.* **2013**, *169*, 1133-40, https://doi.org/10.1111/bjd.12544.
27. Klein, M.; Jarosová, K.; Forejtová, S.; Bečvář, R.; Sedová, L.; Pavelka, K.; Simková, G.; Svobodová, R.; Hviscová, K.; Mann, H.; Půtová, I.; Vencovský, J.; Quantiferon, T.B. Gold and tuberculin skin tests for the detection of latent tuberculosis infection in patients treated with tumour necrosis factor alpha blocking agents. *Clin Exp Rheumatol.* **2013,** *31*, 111-7.
28. Lee, S.K.; Kim, S.Y.; Kim, E.Y.; Jung, J.Y.; Park, M.S.; Kim, Y.S.; Kim, S.K.; Chang, J.; Kang, Y.A. Mycobacterial Infections in Patients Treated with Tumor Necrosis Factor Antagonists in South Korea. *Lung.* **2013**, *191*, 565-71, https://doi.org/10.1007/s00408-013-9481-5.
29. Bermejo, F.; Algaba, A.; Chaparro, M.; Taxonera, C.; Garrido, E.; García-Arata, I.; Guerra, I.; Gisbert, J.P.; Olivares, D.; de-la-Poza, G.; López-Sanromán, A. How frequently do tuberculosis screening tests convert in inflammatory bowel disease patients on anti-tumour necrosis factor-alpha? A pilot study. *Dig Liver Dis.* **2013,** *45*, 733-7, https://doi.org/10.1016/j.dld.2013.03.005.
30. Kim, H.C.; Jo, K.W.; Jung, Y.J.; Yoo, B.; Lee, C.K.; Kim, Y.G.; Yang, S.K.; Byeon, J.S.; Kim, K.J.; Ye, B.D.; Shim, T.S. Diagnosis of latent tuberculosis infection before initiation of anti-tumor necrosis factor therapy using both tuberculin skin test and QuantiFERON-TB Gold In Tube assay. *Scand J Infect Dis.* **2014,** *46*, 763-9, https://doi.org/10.3109/00365548.2014.938691.
31. Lee, H.; Park, H.Y.; Jeon, K.; Jeong, B.H.; Hwang, J.W.; Lee, J.; Cha, H.S.; Koh, E.M.; Kang, E.S.; Koh, W.J. QuantiFERON-TB Gold In-Tube assay for screening arthritis patients for latent tuberculosis infection before starting anti-tumor necrosis factor treatment. *PLoS One*. **2015**, *10*, e0119260, https://doi.org/10.1371/journal.pone.0119260.
32. Kurti, Z.; Lovasz, B.D.; Gecse, K.B.; Balint, A.; Farkas, K.; Morocza-Szabo, A.; Gyurcsanyi, A.; Kristof, K.; Vegh, Z.; Gonczi, L.; Kiss, L.S.; Golovics, P.A.; Lakatos, L.; Molnar, T.; Lakatos, P.L. Tuberculin Skin Test and Quantiferon in BCG Vaccinated, Immunosuppressed Patients with Moderate-to-Severe Inflammatory Bowel Disease. *J Gastrointestin Liver Dis*. **2015**, *24*, 467-72, https://doi.org/10.15403/jgld.2014.1121.244.bcg.
33. Cekic, C.; Aslan, F.; Vatansever, S.; Topal, F.; Yüksel, E.S.; Alper, E.; Dallı, A.; Ünsal, B. Latent tuberculosis screening tests and active tuberculosis infection rates in Turkish inflammatory bowel disease patients under anti-tumor necrosis factor therapy. *Ann Gastroenterol*. **2015**, *28*, 241-246.
34. Baričević, D.; Grle, S.P.; Vergles, J.M.; Čavka, S.C.; Jakopović, M.; Redžepi, G.; Boras, Z.; Baričević, M.; Samaržija, M. Quantiferon-TB gold in-tube test in the diagnosis of latent tuberculosis infection in arthritis patients treated with tumor necrosis factor antagonists. *Acta Clin Croat.* **2017**, *56*, 203-209, https://doi.org/10.20471/acc.2017.56.02.02.
35. Jo, K.W.; Hong, Y.; Jung, Y.J.; Yoo, B.; Lee, C.K.; Kim, Y.G.; Yang, S.K.; Byeon, J.S.; Kim, K.J.; Ye, B.D.; Lee, S.D.; Kim, W.S.; Kim, D.S.; Shim, T.S. Incidence of tuberculosis among anti-tumor necrosis factor users in patients with a previous history of tuberculosis. *Respir Med.* **2013**, *107*, 1797-802, https://doi.org/10.1016/j.rmed.2013.08.011.
36. Abreu, C.; Afonso, J.; Camila, D.C.; Ruas, R.; Sarmento, A.; Magro, F. Serial Tuberculosis Screening in Inflammatory Bowel Disease Patients Receiving Anti-TNFalpha Therapy. *J Crohns Colitis.* **2017,** *11*, 1223-1229, https://doi.org/10.1093/ecco-jcc/jjx080.
37. Kim, E.S.; Song, G.A.; Cho, K.B.; Park, K.S.; Kim, K.O.; Jang, B.I.; Kim, E.Y.; Jeon, S.W.; Lee, H.S.; Yang, C.H.; Lee, Y.K.; Lee, D.W.; Kim, S.K.; Kim, T.O.; Lee, J.; Kim, H.W.; Jee, S.R.; Park, S.J.; Kim, H.J. Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. *World J Gastroenterol.* **2015**, *21*, 3308-16, https://doi.org/10.3748/wjg.v21.i11.3308.
38. Mínguez, S.; Latorre, I.; Mateo, L.; Lacoma, A.; Diaz, J.; Olivé, A.; Domínguez, J. Interferon-gamma release assays in the detection of latent tuberculosis infection in patients with inflammatory arthritis scheduled for anti-tumour necrosis factor treatment. *Clin Rheumatol.* **2012**, *31*, 785-94, https://doi.org/10.1007/s10067-012-1938-z.
39. Vassilopoulos, D.; Tsikrika, S.; Hatzara, C.; Podia, V.; Kandili, A.; Stamoulis, N.; Hadziyannis, E. Comparison of two gamma interferon release assays and tuberculin skin testing for tuberculosis screening in a cohort of patients with rheumatic diseases starting anti-tumor necrosis factor therapy. *Clin Vaccine Immunol.* **2011**, *18*, 2102-8, https://doi.org/10.1128/CVI.05299-11.

40. Costantino, F.; de Carvalho, B.M.; Rat, A.C.; Loeuille, D.; Dintinger, H.; Béné, M.C.; Faure, G.; Chary-Valckenaere, I. Screening for latent tuberculosis infection in patients with chronic inflammatory arthritis: discrepancies between tuberculin skin test and interferon-gamma release assay results. *J Rheumatol.* **2013,** *40*, 1986-93, https://doi.org/10.3899/jrheum.130303.
41. He, D.; Bai, F.; Zhang, S.; Jiang, T.; Shen, J.; Zhu, Q.; Yue, T.; Shao, L.; Gao, Y.; Feng, Y.; Weng, X.; Zou, H.; Zhang, Y.; Zhang, W. High incidence of tuberculosis infection in rheumatic diseases and impact for chemoprophylactic prevention of tuberculosis activation during biologics therapy. *Clin Vaccine Immunol.* **2013**, *20*, 842-7, https://dx.doi.org/10.1128%2FCVI.00049-13.
42. Jung, Y.J.; Lyu, J.; Yoo, B.; Lee, C.K.; Kim, Y.G.; Yang, S.K.; Byeon, J.S.; Kim, K.J.; Ye, B.D.; Lee, K.H.; Lee, S.D.; Kim, W.S.; Kim, D.S.; Shim, T.S. Combined use of a TST and the T-SPOT®.TB assay for latent tuberculosis infection diagnosis before anti-TNF-α treatment. *Int J Tuberc Lung Dis.* **2012**, *16*, 1300-6, https://doi.org/10.5588/ijtld.12.0004.
43. Singanayagam, A.; Manalan, K.; Sridhar, S.; Molyneaux, P.L.; Connell, D.W.; George, P.M.; Kindelerer, A.; Seneviratne, S.; Lalvani, A.; Wickremasinghe, M.; Kon, O.M. Evaluation of screening methods for identification of patients with chronic rheumatological disease requiring tuberculosis chemoprophylaxis prior to commencement of TNF-alpha antagonist therapy. *Thorax.* **2013,** *68*, 955-61, https://doi.org/10.1136/thoraxjnl-2013-203436.
44. Jung, Y.J.; Lee, J.Y.; Jo, K.W.; Yoo, B.; Lee, C.K.; Kim, Y.G.; Yang, S.K.; Byeon, J.S.; Kim, K.J.; Ye, B.D.; Lee, K.H.; Lee, S.D.; Kim, W.S.; Kim, D.S.; Shim, T.S. The 'either test positive' strategy for latent tuberculous infection before anti-tumour necrosis factor treatment. *Int J Tuberc Lung Dis.* **2014,** *18*, 428-34, https://doi.org/10.5588/ijtld.13.0644.