The Assessment of Latent Tuberculosis Prevalence in Patients Treated with Tumor Necrosis Factor Alpha Antagonists

Tümör Nekrozis Faktör Alfa Antagonistleri ile Tedavi Edilen Hastalarda Latent Tüberküloz Prevelansı Değerlendirilmesi

Meltem VURAL[1], Cemal BES[2], Belgin ERHAN[1], Berrin GÜNDÜZ[1]

[1]Istanbul Physical Medicine and Rehabilitation Training Hospital, Department of Physical Medicine and Rehabilitation, Istanbul

[2]Bakırköy Dr. Sadi Konuk Training Hospital, Department of Rheumatology, Istanbul

Yazışma adresi: Meltem VURAL, İstanbul Fizik Tedavi Rehabilitasyon Eğitim ve Araştırma Hastanesi. Adnan Kahveci Bulvarı. 34147 Bahçelievler/İstanbul Tel: 0 212 4422200, Fax: 0 212 4417083, e-mail: drmeltemvural@gmail.com

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Abstract

Background: Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine, which plays an important role in the pathogenesis of several inflammatory diseases such as ankylosing spondylitis (AS), rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Anti-TNF-α therapy is now widely used for treatment of inflammatory diseases. An increased incidence of tuberculosis in patients under anti-TNF-α therapy has been reported. The aim of this study was to investigate the prevalence of latent tuberculosis in patients treated with an anti-TNF-α agent.

Methods: Eighty three patients under anti-TNF-α treatment referring to the Rheumatology outpatient clinic enrolled in the study. Tuberculin skin test (PPD) and chest x-ray are performed. An induration of 5 mm or more is defined as latent tuberculosis. Patients with latent tuberculosis are treated with isoniazid (INH) 300 mg/day during 9 months.

Results: Mean age of the 83 patients was 37.59±10.80 years; the average duration of illness was 9.82±7.08 years. The primary disease was AS (n=62), RA (n=16), and PsA (n=5). The patients were treated with different anti-TNF-α agents (etanercept n=30, adalimumab n=30, infliximab n=21, and golimumab n=2). PPD induration of 5 mm or more was measured in 63 (76%) of 83 patients. INH prophylaxis was started in 76 of the patients including 13 patients with PPD induration < 5mm due to increased risk of tuberculosis (family history, working as a health professional, history of infected with mycobacterium tuberculosis). The number of male patients (76%) with PPD induration ≥5 mm is significantly higher than the number of female patients (24%) with PPD induration ≥5 mm (p=0.026). The number of patients with AS in patients with PPD induration ≥5 mm (n=51, 81%) is significantly higher than the number of patients with AS in patients with PPD induration <5 mm (n=11, 55%) and the presence of RA in patients with PPD induration ≥5mm (n=8, 13%) is found significantly lower than in patients with PPD induration <5mm (n=8, 40%) (p=0.025). There is no statistically significant difference based on used anti-TNF-α between patients with PPD induration ≥5mm and PPD induration <5mm (p=0,369). The rate of PPD induration ≥5 mm in patients treated with infliximab is found 2.4 times more than the other anti-TNF-α agent.

Conclusions: Active tuberculosis or reactivation of latent tuberculosis presents as a serious complication in patients receiving anti-TNF-α therapy. Latent tuberculosis screening and preventive tuberculosis treatment is important before the use of anti-TNF-α agent. Further studies on this subject are needed.

Key words: Anti-TNF-α therapy, latent tuberculosis, PPD

Özet

Amaç: Tümör nekrozis faktör-α (TNF-α) ankilozan spondilit (AS), romatoid artrit (RA) ve psöriatik artrit (PsA) gibi birçok inflamatuar hastalık patogenezinde rol oynayan bir proinflamatuar sitokindir. Anti-TNF-α tedavisi inflamatuar hastalıkların tedavisinde halen yaygın olarak kullanılmaktadır. Anti-TNF-α tedavisi alan hastalarda tüberküloz ve bazı fırsatçı enfeksiyonların sıklığının arttığı bildirilmiştir. Bu çalışmada anti-TNF-α ajanları ile tedavi edilen hastalarda latent tüberküloz prevalansının araştırılması amaçlanmıştır.

Materyal ve Metod: Çalışmaya Romatoloji polikliniğine başvuran ve anti-TNF-α tedavisi alan 83 hasta çalışmaya dahil edildi. Hastalara tuberkülin cilt testi (PPD) yapıldı ve akciğer grafisi çekildi. 5 mm ve üzeri endurasyon saptanan hastalar latent tüberküloz olarak kabul edildi. Latent tüberküloz saptanan hastalara izoniazid (INH) tedavisi 300 mg/gün olarak başlandı ve 9 ay sürdürüldü.

Bulgular: Çalışmaya alınan 83 hastanın (25 kadın, 58 erkek) yaş ortalamaları 37,59±10,80 yıl olup, ortalama hastalık süresi 9,82 ± 7,08 yıl idi. Primer hastalık olarak AS (n=62), RA (n=16) ve PsA (n=5) mevcuttu. Hastalar farklı anti-TNF-α ajanlar (etanercept n=30, adalimumab n=30, infliksimab n=21 ve golimumab n=2) ile tedavi edilmişlerdi. 83 hastanın 63'ünde (% 76) PPD 5 mm ve üzeri olarak tespit edildi. INH profilaksisi PPD 5 mm'nin altında olup sağlık çalışanı olmak, geçirilmiş mikobakterium tüberkülozis ile enfeksiyon veya aile öyküsü gibi artmış tüberküloz riski olan 13 hastanın da dahil olduğu 76 hastaya başlandı. PPD endurasyonu ≥5 mm olan erkek hasta mevcudiyeti (%76) kadınlardan (%24) istatistiksel olarak anlamlı derecede yüksek bulunmuştur (p=0,026).

PPD endurasyonunun ≥5 mm olduğu olgularda AS varlığı (n=51,%81), PPD endurasyonu <5 mm olanlardan (n=11,%55) istatistiksel olarak anlamlı derecede yüksek bulunmuştur. PPD endurasyonu ≥5 mm olanlarda RA varlığı (n=8, %13) PPD endurasyonu <5 mm olanlardan (n=8, %40) istatistiksel olarak anlamlı derecede düşük bulunmuştur (p=0,025). PPD endurasyonu ≥5 mm ve < 5 mm olan hastaların kullandığı anti-TNF-α dağılımında istatistiksel olarak anlamlı farklılık gözlenmemiştir (p=0,369). İnfliximab tedavisi alan hastalarda PPD endurasyonu ≥5mm olanlar diğer ilaç tedavisi alan hasta gruplardan 2,4 kat daha fazla saptanmıştır.

Sonuç: Anti-TNF-α tedavisi bazı romatizmal hastalıkların tedavisinde en etkili yöntemlerdendir. Aktif tüberküloz veya latent tüberkülozun reaktivasyonu anti-TNF-α tedavisi alan hastalarda ciddi bir komplikasyon olarak ortaya çıkar. Bizim hasta populasyonumuzda latent tüberküloz yaygın olup, hastalarımız profilaktik INH tedavisi almışlardı. Anti-TNF-α tedavisi öncesi latent tüberküloz taranması ve önleyici tüberküloz tedavisi önemlidir. Bu konuda daha fazla çalışmalara gereksinim vardır.

Anahtar kelimeler: Anti-TNF-α tedavisi, latent tüberküloz, PPD

Introduction

Tumor necrosis factor-α (TNF-α) is a cytokine which plays an important role in the in the pathogenesis of several rheumatic diseases (1, 2). TNF-α, stimulates the secretion of inflammatory cytokines. This function regulates the initiation and continuation of the inflammatory reactions (3). The efficacy of the anti-TNF-α agents in the

treatment of inflammatory diseases such as ankylosing spondylitis (AS), rheumatoid arthritis (RA) and psoriatic arthritis (PsA) has been demonstrated in numerous trials (4, 5, 6). The anti-TNF-α agents have revealed rapid and consistent therapeutic responses. However, some of patients fail to respond to anti-TNF-α treatment or experience side effects (5). In patients receiving anti-TNF-α treatment there is an increased risk of reactivating infections such as tuberculosis (2, 7). The increase of reactivation tuberculosis associated with anti-TNF-α treatment has led to a demand to screen for active and latent tuberculosis in patients before anti-TNF-α agent is given (2, 7). In addition, screening of the patients included their history of exposure to Mycobacterium tuberculosis, clinical examination, PPD and chest X-ray (2). Different recommendations for targeting patients with latent tuberculosis infection have been advised worldwide by scientific organizations and certain consensus to decrease the risk of active tuberculosis (8, 9, 10). These recommendations for the screening and treatment of patients with latent tuberculosis infection who were going to be treated with TNF-α antagonists (11).

The use of TNF antagonists is accompanied by an increased risk of active tuberculosis and different risk rates are poorly understood. Anti-TNF-α agents are also used in different societies, the risk of development of infection varies (11, 12, 13).

Studies have investigated different risk rates PPD which used in screening for latent tuberculosis between gender, patient's current rheumatic disease and anti-TNF-α agents (14, 15).

In this study we aimed to investigate the prevalence of latent tuberculosis in patients treated with anti-TNF-α. In addition, we studied the relationship between such as type of rheumatic disease, the type of anti-TNF-α agent and gender features in patients with PPD induration of 5 mm or more and less than 5 mm.

Methods

Eighty three patients under anti-TNF-α treatment from the Rheumatology department of a training hospital in Istanbul from February 2012 to June 2013 who suffered from AS, RA and PsA were included in this retrospective study. For each patient we collected information including sex, age, diagnosis, date of diagnosis and type of anti-TNF-α treatment, duration of illness.

The presence of latent tuberculosis was assessed by medical history, PPD and chest x-ray. The evaluation of the medical history included current symptoms, prior history of treatment for tuberculosis, working as a health professional, family history and close contact with active pulmonary tuberculosis within the last year.

The PPD was performed on the volar side of the forearm according to the Mantoux method. A 2 tuberculin unit's dose (0.1 ml) of tuberculin purified derivative was given intradermal administration. The transverse diameter of the induration was measured 72 hours later. The PPD was repeated 1 to 3 weeks later in subjects with negative initial PPD results (2). A positive PPD was defined as an induration of 10 mm in diameter. A boosted reaction was described as induration size of 10 mm on the first PPD and an induration size of 10 mm on the second PPD (16). An induration of 5 mm or more is defined as latent tuberculosis. Patients with latent tuberculosis are treated with isoniazid (INH) 300 mg/day during 9 months (2). In addition, a negative PPD result with an active tuberculosis lesion on chest x-ray, a recent contact with patients having active pulmonary tuberculosis and health professionals at risk for tuberculosis were considered AS an indication for latent tuberculosis treatment (1, 11).

Statistical methods

In this study, statistical analyses were carried out using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) software package. In order to evaluate statistical data, descriptive statistical methods (mean, standard deviation) were used as well as independent t-test for comparison between two groups, chi-square test for comparison of quantitative data. Odds ratios (OR) and their accompanying 95% confidence intervals (CI) were estimated from the multivariate logistic regression model. Results were evaluated considering the significance level $p < 0.05$.

Results

Mean age of the 83 patients (26 female, 58 male) was 37.59±10.80 years. The primary disease was AS (n=62, 74.70%), RA (n=16, 19.28%), and PsA (n=5, 6.02%). The patients were treated with different anti-TNF-α agents (etanercept n=30, adalimumab n=30, infliximab n=21, and golimumab n=2). PPD induration of 5 mm or more was measured in 63 (76%) of 83 patients. INH prophylaxis was started in 76 of the patients including 13 patients with PPD induration < 5mm due to increased risk of tuberculosis (family history, working as a health professional, history of infected with mycobacterium tuberculosis). The average duration of illness was 9.82±7.08 (min: 1, max: 31) years. No statistically significant difference was observed between average durations of the illness and mean age of the patients with PPD induration of 5 mm or more and less than 5 mm (p=0,124, p=0,956 respectively). The number of male patients (n=48, 76.19%) with PPD induration ≥5 mm is significantly higher than the number of female patients (n=15, 23.81%) with PPD induration ≥5 mm (p=0.026). The rate of PPD induration ≥5 mm in male patients is found 3.2 times more than the rate of female patients.

The number of patients with AS in patients with PPD induration ≥5 mm (n=51, 80.95%) is significantly higher than the number of patients with AS in patients with PPD induration <5 mm (n=11, 55%) and the presence of RA in patients with PPD induration ≥5mm (n=8, 12.7%) is found significantly lower than in patients with PPD induration <5mm (n=8, 40%) (p=0.025). The rate of PPD induration ≥5 mm in patients with AS is found 3.48 times more than the patients with RA or PsA.

There is no statistically significant difference based on used anti-TNF-α between patients with PPD induration ≥5mm and PPD induration <5mm (p=0,369). The rate of PPD induration ≥5 mm in patients treated with infliximab is found 2.4 times more than the other anti-TNF-α agent.

Discussion

TNF-α plays a critical role in the pathogenesis of some rheumatic diseases (2). In recent years, TNF-α inhibitors are used for the treatment of chronic inflammatory diseases such as AS, RA and PsA (2, 17). On the other hand, anti-TNF-α plays a critical role in host defense against bacterial infectious diseases, and in particular of mycobacterial infections. Studies of anti-TNF-α therapy support the complications associated with the use of anti-TNF-α agents, particularly the risk of serious infections (12, 17, 18). Active tuberculosis or reactivation of latent tuberculosis infection has been associated in patients with rheumatologic diseases under anti-TNF-α treatment (2, 8).

Latent tuberculosis is condition in which a person is infected with Mycobacterium tuberculosis, but does not have active tuberculosis disease (19). The identification and treatment of latent tuberculosis are crucial for the elimination of tuberculosis (20). The active tuberculosis or reactivation of latent tuberculosis associated with anti-TNF-α therapy has led to a demand to screen the patients before anti-TNF-α treatment is given (7).

In Turkey, active tuberculosis incidence rate of 27 per 100 000 population was reported (21). The prevalence of latent tuberculosis is unknown due to the PPD in a population that is immunized for Bacille Calmette-Guérin (BCG) vaccine (22). BCG vaccine is administered for the prevention and control of tuberculosis in developing countries with high-risk like in our country. BCG is performed routinely, that's why BCG vaccination history should not be considered while evaluating PPD (23). The effect of BCG vaccination on positive PPD in adults ages is most likely insignificant. Furthermore positive PPD response and positive retest in adults is caused by latent tuberculosis rather than previous vaccination in developing countries with a high prevalence of tuberculosis (24). In a population with a high incidence, this may represent a true prior exposure to Mycobacterium infection rather than BCG vaccination (11).

Some literature suggests that 9 months of treatment with INH does not fully protect against the development of active tuberculosis, although the decrease in the rate is 70% (20, 25). This rate may be caused by some patients did not complete 9 months of INH therapy due to intolerance; instead they were treated with rifampicine and pyrazinamide (8). Consequently, it is recommended that patients should be treated for 9 months with INH because of the high tuberculosis risk detected and these recommendations are based on various guidelines and consensus (8). Similarly, the recommendation that a finding of 5 mm on the PPD should be an indication for treatment with INH (300 mg/day) for 9 months in our country (12). Nevertheless, according to the risk determined by the physician for the patient, in spite of 0-4 mm PPD result, treatment of latent tuberculosis infection could be started (26).

INH prophylaxis is recommended for health professional those who are at high risk for tuberculosis, family history of tuberculosis and close contact with a patient having active tuberculosis in the last year (26). Therefore, it must be interrogated certain factors such as tuberculosis history of individuals around the patient's environment and patient's own history. In our study, we started INH prophylaxis to 13 patients with PPD induration of less than 5 mm whom were thought to be at risk for tuberculosis.

Retrospective cohort study was conducted in healthy subjects with PPD screening for tuberculosis; there was no significant relationship between gender and PPD (27). However, we found that the rate of PPD induration ≥5 mm in male patients 3.2 times more than female patients in our study. Laurenti et al. (28) demonstrated that the rate of latent tuberculosis in male patients 3.72 times more than female patients. In another study, it was indicated that the rate of latent tuberculosis in male patients 6.81 times more than female patients (29).

Kim et al. (16) determined that the rate of PPD induration ≥5 mm in male patients was 1.78 times more than the female patients. Jimenez-Corona et al. (30) interpreted that gender-related differences in tuberculosis incidence rates of the general population may be associated with the environmental exposure and dynamics of local dissemination.

In another study, it was found that tuberculosis infection in men more than women. The investigators stated that, this situation due to neglect of preventive measures and social reasons such as spend more time in crowded places and smoking (31).

Pamuk et al. (15) reported the number of PPD positivity in AS patients was statistically higher than RA patients. Similarly, we determined the number of AS with PPD induration ≥5 mm in cases significantly higher than the number of AS with PPD induration <5 mm. Furthermore, we found the number of PPD induration ≥5 mm in patients with AS more than the

patients with RA or PsA. Karkucak et al. (32) reported that the value of PPD induration in patients with AS was higher than the patients with RA. Hanta et al. (14) determined that there was no significant difference between AS and RA patients with PPD induration of 5 mm or more. In another study, investigators indicated that there was no statistically significant difference in terms of PPD positivity between patients with AS and RA. In addition, there was no difference in terms of PPD positivity in patients with RA and PsA (33). In our study, we found that there was no statistically significant difference in patients with PPD induration ≥5mm between patients with RA and PsA. However, the rate of PPD induration ≥5 mm in patients with AS was found 3.48 times more than the patients with RA or PsA. Nobre et al. (34) reported that the PPD positivity in patients with RA was lower than the patients with RA and PsA treated with infliximab. The investigators suggested that PPD had a low sensitivity for detection of latent tuberculosis in RA patients. In another study, it was determined that the value of PPD was lower in patients with RA than the patients with AS and PsA. In this study, the investigators emphasized that PPD had limited value for determination of tuberculosis infection in candidates to infliximab treatment (35). Carmona et al. (8) suggested that the risk of tuberculosis should be evaluated and updated the recommendations.

It has been indicated that TNF antagonist therapy related increased risk of active tuberculosis; there were increased ratio for infliximab than etanercept or for adalimumab. Nevertheless, direct comparison has not been reported (8). On the other hand, active tuberculosis cases might be occurred in patients treated with other anti-TNF-α agents (11). We found that there was no statistically significant difference based on used anti-TNF-α between patients with PPD induration ≥5 mm and PPD induration <5mm. In addition, we determined the rate of PPD induration ≥5 mm in patients treated with infliximab was 2.4 times more than the other anti-TNF-α agent. Despite INH prophylaxis, it is open to debate whether patients treated with infliximab and having an induration of 5 mm or more needs a frequent follow-up or not. Gómez-Reino et al. (11) stated that there was no difference in the prevalence of active tuberculosis in patients treated with anti-TNF-α agents. Therefore, patients should be monitored with the same sensitivity that are going to be treated with all anti-TNF-α agents for latent tuberculosis detection and prevention of the development of active tuberculosis.

Our study had some limitations. We could not easily differentiate PPD reactions due to other environmental mycobacteria such as Mycobacterium bovis. People are most commonly infected with Mycobacterium bovis by eating or drinking contaminated, unpasteurized dairy products. In an M. bovis infected individual, a PPD induration of 5 mm or more is considered positive. Another limitation of the present study was its relatively low sample size.

In conclusion, active tuberculosis or reactivation of latent tuberculosis is a serious problem in patients treated with anti TNF-α. Latent tuberculosis screening and preventive tuberculosis treatment is important in populations with high incidence rates of tuberculosis before the initiation of anti-TNF-α treatment. Different mechanisms of action of current anti-TNF-α agents and their effects on different diseases might be associated with reactivation of latent tuberculosis. Further studies on this subject are needed to develop new strategies in screening methodologies for latent tuberculosis and preventive approaches for anti-TNF-α agents related tuberculosis infections.

Table 1. Characteristics of the patients treated with anti tumor necrosis factor (TNF) alpha agents

		N	%	Mean	SD
Gender	Male	58	69.88%		
	Female	25	30.12%		
Diagnosis	AS	62	74.70%		
	RA	16	19.28%		
	PsA	5	6.02%		
TST (mm)	<5 mm	20	24.09%		
	?5 mm	63	75.91%		
Anti -TNF-α agents	Etanercept	30	36.14%		
	Infliximab	21	25.30%		
	Adalimumab	30	36.14%		
	Golimumab	2	2.41%		
Age (year)		83		37.59	10.80
Duration of illness (year)		83		9.82	7.08
TST (mm)		83		8.38	5.71

NOTE: Values expressed as mean ± SD, TNF: tum or necrosis factor, TST: tuberculin skin test, AS: Ankylosing spondylitis, RA: rheumatoid arthritis, PsA: psoriatic arthritis

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