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Variations of tuberculin skin test in patients with rheumatologic disorders and under anti-TNF treatment

Anti-TNF tedavisi uygulanan romatoloji hastalarında Tüberkülin deri testi seviyelerinin değişimi

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Abstract

Aim: Nowadays PPD is the most inexpensive and easy to apply modality of test in identification of latent tuberculosis infection. Isoniazid (INH) prophylaxis must be given before usage of anti-TNF-α agents for patients. We aimed to investigate the change in Tuberculin skin test (TST) levels and Isoniazid (INH) prophylaxis rates in patients with inflammatory rheumatic diseases treated with anti-tumor necrosis factor alpha (TNF-α) agents.

Methods: A cross-sectional study was planned. Patients with inflammatory rheumatic diseases treated with anti-TNF agents were included in the study. Demographic data, initial TST level and INH prophylaxis had obtained from patient's files. Control TST tests had done at tuberculosis dispensaries in different time periods such as 1-2 / 2-3 / 3-4 / ≥4 years of anti TNF treatment. INH prophylaxis rates according to initial and control TST tests were compared. The relationship between INH prophylaxis and duration of anti-TNF therapy were examined.

Results: A total of 117 patients were included in the study. The mean age of the patients (81 male, 36 female) was 40.4±12.90. The control TST levels was significantly higher than initial TST (p=0.001). INH prophylaxis was given to total 99 (84.6%) of 117 patients (to 63 (53.8%) according to initial and to 36 (30.8%) according to control TST tests). There was no relationship between duration of anti TNF therapy and INH prophylaxis initiation (p=0.180).

Conclusion: Anti-TNF treatments may reduce the rates of false-negative TST in patients with rheumatic diseases and latent tuberculosis (LTBI) at any stage of the treatment. Therefore, LTBI, which is not determined with initial TST tests, may be determined with TST test applied in the later stages of anti-TNF treatment, and the risk of active tuberculosis can be reduced by INH prophylaxis in this patients.

Keywords: Tumor necrosis factor inhibitors, Rheumatic diseases, Tuberculin skin test, Tuberculosis, Minor side effect

Öz

Giriş: Günümüzde Latent tüberküloz tanısında kullanılan en ucuz ve kolay uygulanan test PPD'dir. Öneriler doğrultusunda anti TNF ajanlarla tedavi öncesi izoniazid (İNH) profilaksisi verilmektedir.

Amaç: Çalışmamızda anti TNF-α tedavisi alan enflamatuvar romatizmal hastalığı olan hastalarda tedavi öncesi tüberkülin deri testi (PPD) düzeyleri ve anti TNF-α tedavisi sırasındaki kontrollerde tekrarlanan PPD düzeyindeki değişimleri değerlendirilmesi amaçladık.

Yöntemler: Çalışamaya anti-TNF tedavisi alan enflamutuvar romatizmal hastalığı olan toplam 117 hasta dahil edilmiştir. Anti TNF ilaç kullanan hastaların tedavi öncesi rutin olarak bakılan PPD düzeyleri, kontrollerde tekrarlanan PPD değişimleri, başlangıç ve kontrol PPD sonuçlarına göre İNH profilaksisi başlanma oranları değerlendirildi.

Bulgular: Çalışmamızda anti TNF ilaç kullanan 117 hastanın yaş ortalaması (81 erkek, 36 kadın) 40.4±12.90. Anti TNF ilaç kullanımı sonrası kontrol PPD ortalamasında başlangıç PPD seviyeleri ortalamasına göre istatistiksel olarak anlamlı bir artış saptandı. (p=0,001) Çalışmamıza alınan 117 hastanın 99'una (%84,6) İNH profilaksisi verilmiş, İNH profilaksisi verilen 99 hastanın 63'üne (%53) başlangıç PPD sonucuna göre, kalan 54 hastanın ise 36'sına (%30) daha kontrol PPD sonucuna göre İNH profilaksisi verildiği görüldü. Kontrol PPD sonucuna göre İNH profilaksisi başlanması ile hastalık tanısı ve kullanılan anti TNF ilaç çeşidi arasında anlamlı bir ilişki saptanmadı. (p=0,18)

Sonuç: Anti-TNF ilaç tedavisi alan romatizmal hastalarda, tedavi sürecinde immun cevabın düzenlenmesi ile PPD düzeyini değiştirip yalancı negatiflik oranını azaltabilir. Bu yüzden proflaksi alması gereken hastaları belirlemek için tedavinin ileri dönemlerinde de belli aralıklarla PPD testi tekrarlanması ve hastaların profilaksi açısından tekrar değerlendirilmesi önerilebilir.

Anahtar kelimeler: Tumor nekroz faktör inhibitörü, Romatolojik hastalık, Tüberkülin deri testi, tüberküloz, Yan etki

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Introduction

Tumor necrosis factor alpha (TNF-α) is a cytokine that holds important place in the pathogenesis of inflammatory rheumatic diseases [1,2]. In recent years, biological agents acting by blocking the effect of TNF-α had been used with success in the treatment of rheumatic diseases.

Following the widespread use of anti TNF therapy, the high incidence of active tuberculosis (TB) was reported in patients treated with anti TNF, which is usually associated with the reactivation of latent tuberculosis infection (LTBI) [3,4]. Afterwards, the screening of LTBI began to be performed before initiation of anti-TNF treatment [5]. Tuberculin skin test (TST) is the most widely used test for identification of LTBI, but TST is affected by immunosuppressive therapy and inflammatory disorders [4,6-8]. Therefore, TST values in patients with inflammatory rheumatic diseases may change during the anti-TNF treatment process [9,10]. In literature, there are few studies that evaluate the TST response in the patients receiving short-term anti TNF treatment. Herewith, to the best knowledge of the authors, a study investigating changes in TST levels in the later years of anti TNF treatment is not available in the literature.

We aimed to investigate the changes of the TST levels and prophylaxis initiation rates into the later years of anti TNF treatment in patients taking anti TNF therapy for inflammatory rheumatic diseases more than a year.

Materials and methods

In this study, patients who were followed between 2005 and 2013 at rheumatology clinic and diagnosed as rheumatologic disorders were included. Patients who had malignancies, solid tumors and active infection were excluded. Patients were informed about the study procedure and they consented to participate. Local ethics committee approved the study protocol.

Demographic data, diagnoses, diagnosis time, anti TNF drug duration, initial TST level, control TST level, control TST time and INH prophylaxis had obtained retrospectively from patient files. TST tests had done at tuberculosis dispensaries. Measured TST results were divided into two groups: TST negative (0 to 4 mm), and TST positive (≥ 5 mm). INH prophylaxis were started to the patients with TST≥5mm or TST=0 in 2 repeats. INH prophylaxis as started by the initial and control TST level were recorded. Also, control TST times were assessed into 4 groups as 1-2 / 2-3 / 3-4 / ≥4 years of anti TNF treatment (Figure 1).

Statistical analysis

All statistical data was analyzed using the program PASW 18 (SPSS / IBM, Chicago, IL, USA). To define the sample, descriptive statistics like frequency distribution, mean, standard deviation were used. In cases where the assumptions of parametric tests provided, the average difference of two independent groups was determined via "Student t test", difference between more than two groups was determined via "variance analysis". In cases where the assumptions of parametric tests not provided, nonparametric alternatives; "Mann-Whitney" and "Kruskal-Wallis" tests were used. Categorical data was examined via "chi-square test" or "Fisher's Exact test". To identify differences in analysis, 5% significance level (or margin of error α =0.05) was used.

Results

One-hundred-seventeen patients were included in the study. These were 27 rheumatoid arthritis (RA), 77 ankylosing spondylitis (AS), 6 psoriatic arthritis (PsA), 7 juvenile chronic arthritis (JKA) patients receiving anti TNF treatment for longer than a year, a total of 117 patients were included. Eighty-one (69.2%) of the patients were male, 36 (30.8%) were female. The mean age of the patients was 40.4±12.90 (16-68). Diagnosis and demographic characteristics of patients are summarized in Table 1.

The majority of RA patients were female (16, 59.3%), whereas the majority of AS patients was male (61, 79.2%). While ETA was more in RA patients (40, 52.0%), İNF was more in AS patients (18, 66.7%).

The mean control TST levels were 8.29 ± 6.40 while the mean initial TST levels were 5.87±5.45. The mean of control TST levels was significantly higher than initial (p=0.001) (Table 2).

Table 1: Diagnosis and demographic characteristics of patients

		Mean±SD (Min-Max)
Age (year)		40.4±12.90 (16-68)
How many years patient had the disease?		14.29±6.88 (2-16)
Anti TNF treatment times (years)		4.60±2.02 (1-11)
		n (%)
Female		36 (30.8)
Male		81 (69.2)
Diseases	RA	27 (23.1)
	AS	77 (65.8)
	PsA	6 (5.1)
	JKA	7 (6.0)
Anti TNF drug	IFN	45 (38.4)
	ETA	47 (40.2)
	ADA	25 (21.4)
Anti TNF treatment times	1-2 years	20 (17.1)
	2-3 years	16 (13.7)
	3-4 years	26 (22.2)
	≥4 years	55 (47.0)

SD: Standard deviation

Table 2: The initial and control TST levels and INH prophylaxis rates

	Initial TST (n= 117)	Control TST (n=54)	p	Total INH prophylaxis
TST levels (Mean ± Std)	5.87±5.45	8.29±6.40	0.001*	
0 mm	8 (6.8%)	5 (9.3%)		13
1-4mm	54 (46.2%)	18 (33.3%)		0
≥ 5 mm	55 (47.0%)	31 (57.4%)		86
Total INH prophylaxis	63 (53.8%)	36 (66.7%)		99 (84.6%)

*: p < 0.05

INH prophylaxis was given before starting anti TNF treatment to 63 (53.8%) patients according to initial (TST ≥ 5mm or 2 repeats TST=0). The control TST were converted from negative to positive in 31 (57.4%) and anergy developed in 5 (9.3%) patients of 54 patients not given INH prophylaxis at initial. INH prophylaxis was started in 36 (30.8%) of total 117 patients according to control TST. To total 99 (84.6%) of 117 patients, INH prophylaxis was given (Table 2).

There was no relationship between duration of anti TNF therapy and INH prophylaxis initiation according to control TST levels (p=0.180) (Table 3).

When compared to INH prophylaxis rates according to diagnosis of disease and the anti-TNF drugs, there was no relation between diagnosis of disease and the anti TNF drugs

used with INH prophylaxis initiation (p=0.990, p=0.349) (Table 4).

Table 3: INH prophylaxis initiation according to duration of anti-TNF therapy

Control TST (n=54)	Anti TNF treatment times 1-2 years	2-3 years	3-4 years	≥4 years	p
INH prophylaxis (+) (n=36)	7 (87.5%)	3 (60.0%)	12 (75.0%)	14 (56.0%)	0.18
INH prophylaxis (-) (n=18)	1 (12.5%)	2 (40.0%)	4 (25.0%)	11 (44.0%)	
Total (n=54)	8 (100%)	5 (100%)	16 (100%)	25 (100%)	

Table 4: INH prophylaxis according to diagnosis of disease and the anti-TNF drugs

INH prophylaxis Rates	Diseases						Anti TNF			
	n (%)	RA	AS	PsA	JKA	p	INF	ETA	ADA	p
İnitiation	63 (53.8%)	12	43	4	4	-	26	19	18	-
Control	36 (30.8%)	9	23	2	2	0.98	14	18	4	0.15
Total	99 (84.4%)	21	66	6	6	0.99	40	37	22	0.35

Discussion

In this study where we aimed to evaluate the changes in TST levels during anti TNF treatment in patients with inflammatory rheumatic diseases, we found that the mean of control TST levels were significantly increased compared to initiation TST levels and INH prophylaxis to one of three patients was started according to their control TST results. But, there was no relationship between INH prophylaxis and duration of anti-TNF therapy.

After anti TNF agents came into use, TB cases started to be reported among the patients who were under anti TNF treatment and studies showed that TB ratio in these patients were more than control groups [10-13]. In 2001, among 147.000 patients treated with Infliximab, 70 TB cases were reported. 2 months later this number had risen to 117. Thus, it has been accepted that these agents increases the risk of developing TB, especially in those who have LTBI [14,15]. The increased TB risk in this patients may be due to blocking TNF-α because it is an effective mediator in the regulation of cellular immune responses [9,16]. It has also been reported that active TB cases can be reduced by 50-90% with the diagnosis and treatment of LTBI [17-19]. Therefore, before anti TNF treatment, all patients are evaluated with TST for LTBI and the patients who develop endurance 5mm or 0mm are given TB prophylaxis. In our study, TST was applied to all of our patients and prophylaxis was initiated in 63 of them.

The TST test is an important technique for predicting active disease in patients with LTBI. However accuracy and reliability of TST is affected by immune suppressive therapy and the activity of underlying inflammatory diseases [20]. İn countries where TB is epidemic, the decreased responses to TST were found in patients diagnosed with RA compared to control groups [21,22]. Sezer et al. [23] have detected that TST levels were higher in healthy controls than in patients with AS and RA. Therefore, among the patients with inflammatory rheumatic diseases, false negative TST results can be said to be higher than the normal population. But, TST levels are expected to increase during treatment in patients taking anti-TNF when the immune system re-regulation and disease remission achieved. Indeed, Çağatay et al. [9] have reported that mean TST levels after 1 year were significantly higher than levels at initiation, and the negative initial TST were converted to positive at 1-year repeat in 26 (30%) patients. Joven at al. [22] have been reported that TST response increased in patients using anti-TNF agent. In a study by Bonfiglioli at al. [24], they reported that the negative initial TST were converted to positive at 5 of 51 patients who had negative TST in 36 months of anti-TNF treatment.

In our study, the mean of control TST levels was significantly higher than initial and INH prophylaxis was started in 36 (30.8%) of total 117 patients according to control TST. The reason for this higher rate from the literature in our study may be that TST was also repeated even in patients in the later stages of treatment and TB prevalence varies among societies. This condition suggests that TST can be transformed into positive at different times in different patients. In our study, all patients could not be evaluated with TST in each year of the treatment process due to retrospective nature of the study. This issue is a major limitation of our study. We think that these results need to be supported with prospective follow-up studies.

Conclusion

Our results support that the immune system re-regulation and disease remission may occur at any stage of the treatment process and may reduce the rates of false-negative TST in patients treated with anti-TNF. Thereby, TST sensitivity rises in patients with LTBI. Consequently, the patients with LTBI not determined with initial TST may be determined with TST test repeated applied in the later stages of anti-TNF treatment and INH prophylaxis reduce the risk of active TB in this patients.

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