Research Article

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Evaluation of tuberculosis frequency in children using biological agents

Biyolojik ajan kullanan çocuklarda tüberküloz sıklığının değerlendirilmesi

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Abstract

Purpose: Anti-TNF drugs increase the risk of tuberculosis. In this study we aimed to investigate the incidence of tuberculosis in patients using anti-TNF drugs.

Materials and methods: One hundred and fifteen pediatric cases which were received anti-TNF drugs were included in the study. The clinical and epidemiological characteristics of the cases were analyzed retrospectively.

Results: One hundred and fifteen cases using anti-TNF drugs were included in the study. The diagnoses of the cases were as follows; Juvenile Rheumatoid Arthritis 76 (66%), Ulcerative Colitis 11 (9.6%), Crohn's 7 (6%), Ankylosing Spondylitis 6 (5.2%), FMF 5 (4.3%), Psoriasis 4 (3.5%). The distribution of the agents used by the patients was; etanercept 74 (64.3%), infliximab 17 (14.8%), adalimumab 17 (14.8%), anakinra 5 (4.3%), and canakinumab 2 (1.7%). It was learned that all cases had BCG vaccinations when they were two months old, confirmed by the vaccination cards and the ministry of health's vaccination follow-up system. TST was performed in all of the cases and TST response was measured as <5mm in 89 (77.4%), 5-9 mm in 11 (8.7%), 10-14 mm in 8 (7.4%), >15 mm in 7 (5.6%) cases. Isoniazid (INH) prophylaxis was started for nine months in 17 cases with the diagnosis of latent tuberculosis. Active tuberculosis was not detected in any of the cases.

Conclusion: All patients receiving anti-TNF need to be evaluated for tuberculosis. Although it is not detected at the beginning of the treatment, regular tuberculosis screening should be continued during the treatment with contact history, symptoms, physical examination, chest X-ray, and TST/IGRA in light of current guidelines.

Key words: Tuberculosis, pediatric, anti-TNF.

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Öz

Amaç: Anti-TNF ilaçlar tüberküloz enfeksiyon riskini arttırırlar. Bu çalışmayla Anti-TNF ilaç kullanan hastalarda, tüberküloz gelişme sıklığını araştırmayı amaçladık.

Gereç ve yöntem: Çalışmaya anti-TNF ilaç kullanan 115 çocuk hasta dahil edildi. Olguların klinik ve epidemiyolojik özellikleri retrospektif olarak değerlendirildi.

Bulgular: Anti-TNF ilaç kullanan 115 olgu çalışmaya dahil edildi. Olguların tanıları; Juvenil Romatoid Artrit 76 (%66), Ülseratif Kolit 11 (%9,6), Crohn's 7 (%6), Ankilozan Spondilit 6 (%5,2), FMF 5 (%4,3), Psoriasis 4 (%3,5) şeklindeydi. Hastaların kullandığı ajanların dağılımı ise; etanersept 74 (%64,3), infliximab 17 (%14,8), adalimumab 17 (%14,8), anakinra 5 (%4,3) ve kanakinumab 2 (%1,7) şeklindeydi. Tüm vakaların iki aylıkken BCG aşısı olduğu öğrenildi, aşı kartları ve sağlık bakanlığının aşı takip sisteminden teyit edildi. Tüm olgulara TDT yapıldı ve TDT yanıtı <5mm 89 (%77,4), 5-9 mm 11 (%8,7), 10-14 mm 8 (%7,4), >15 mm 7 (%5,6) olarak ölçüldü. Latent tüberküloz tanısı alan 17 olguya 9 ay izoniazid (INH) profilaksisi başlandı. Olguların hiçbirinde aktif tüberküloz saptanmadı.

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Sonuç: Anti-TNF alan tüm hastaların tüberküloz açısından değerlendirilmesi gerekmektedir. Tedavi başlangıcında saptanmasa da tedavi süresince güncel kılavuzlar ışığında temas öyküsü, semptomlar, fizik muayene, akciğer grafisi ve TDT/IGRA ile düzenli tüberküloz taramasına devam edilmelidir.

Anahtar kelimeler: Tüberküloz, çocuk, anti-TNF.

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Introduction

Tumor Necrosis Factor-alpha (TNF-alpha) is a proinflammatory cytokine that plays an essential role in the pathogenesis of many inflammatory diseases. TNF-alpha increases the release of many cytokines and chemokines, causing the migration and proliferation of lymphocytes to the inflammation area. In this way, granuloma formation occurs, and even if the bacilli cannot be destroyed, they are imprisoned in this structure, preventing their proliferation and spread [1, 2]. Many studies have shown the importance of TNF-alpha in controlling Mycobacterium species, *Aspergillus fumigatus, Histoplasma capsulatum, Coccidioides species, Toxoplasma gondii, Cryptococcus neoformans, Candida albicans* and viral pathogens [3, 4]. TNF-alpha plays an essential role in the pathogenesis of inflammation in many diseases. Therefore, in recent years, TNF-alpha inhibitors used in the treatment of autoimmune and inflammatory conditions such as Juvenile Idiopathic Arthritis (J.I.A.), Rheumatoid Arthritis (R.A.), Psoriasis, Psoriatic Arthritis, Crohn's Disease, Ankylosing Spondylitis (AS), Familial Mediterranean Fever (FMF), Autoimmune Uveitis, etc. The most commonly used anti-TNF-alpha agents clinically today are infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol [5-8]. Anti-TNF agents are effective in autoimmune diseases by suppressing inflammation. Still, also they increase the risk of granulomatous infections such as *Histoplasma capsulatum*, Nocardia, and especially tuberculosis by preventing granuloma formation, chemotaxis of neutrophils and macrophages, and cytokine release [3, 4].

Tuberculosis is a global public health problem that affects one-third of the world's population and is the second most common cause of death from an infectious disease. Although the primary area of the disease is predominantly the lungs, other organs and systems may also be affected. It has been shown that the use of anti-TNF drugs increases the risk of tuberculosis 11-40 times. Based on this, guidelines on the use of anti-TNF recommend screening for latent tuberculosis infection (LTBI) before anti-TNF therapy and isoniazid (INH) prophylaxis for positive cases [9-11]. During the screening, patients should be evaluated with their medical history, physical examination findings, chest radiographs, and TST or interferon-gamma release assay (IGRA). Furthermore, TNF-alpha inhibitors are contraindicated as soon as active T.B. infection is detected, and anti-TNF therapy should be discontinued immediately if tuberculosis develops during treatment [12]. In this study, we aimed to investigate the risk of tuberculosis development and their follow-up and treatment protocols in pediatric patients using anti-TNF drugs.

Material and method

One hundred and fifteen pediatric cases were followed up in our University Faculty of Medicine, Department of Pediatrics, between January 2011 and December 2021. They received anti-TNF, and biological agent treatment was included in the study. The clinical and epidemiological characteristics of the cases included in the study, the primary disease, the anti-TNF and immunosuppressant agents used and their duration, physical examination and laboratory findings, and TST and IGRA results were analyzed retrospectively. The study was approved by University Medical Ethics Committee (decision no: 32-1542). All cases were followed up for tuberculosis with clinical and physical examination every three months, chest X-ray every six months, and TST test

once a year. The Mantoux method was used for TST. For this purpose, five units of P.P.D. were injected intradermally into the forearm ulnar surface, and the induration's transverse diameter was measured 48-72 hours later. The TST result was evaluated according to the current guideline recommendations of the time it was performed. Induration of 5 mm or more was considered positive in those not vaccinated with BCG, and induration of 10 mm or more in those immunized with BCG. In patients who did not react, the test was repeated ten days later, and the booster effect was evaluated. Results 6 mm larger than the first test or greater than 10 mm were considered positive. IGRA test was performed in cases with negative TST Isoniazid (INH) was used for nine months for prophylactic treatment in patients diagnosed with LTBI.

Statistical analysis

The IBM SPSS Statistics 18 package program was used to analyze the data in the study. Central and prevalence measures such as number, percentage, minimum, maximum values, mean, median, and standard deviation were used to create descriptive statistics, and Pearson, Chi-square, and McNemar tests were used to determine the difference between categorical variables. $p \leq 0.05$ was considered statistically significant.

Results

One hundred fifteen cases using anti-TNF drugs were included in the study. The mean age of the cases was 13 (2-18) years. Of the patients, 66 (57%) were female, and 49 (43%) were male. Of the cases, 76 (66%) had Juvenile Rheumatoid Arthritis, 11 (9.6%) Ulcerative Colitis, 7 (6%) Crohn's, 6 (5.2%) Ankylosing Spondylitis, 5 (4.3%) FMF and 4 of them were followed up due to Psoriasis (3.5%) (Table 1). Etanercept in 74 (64.3%) cases, infliximab in 17 (14.8%) cases, adalimumab in 17 (14.8%) cases, anakinra in 5 (4.3%) cases, and canakinumab was used in 2 (1.7%) cases. In patients with anti-TNF drugs, 66 (57.4%) were using methotrexate, 11 (9.6%) were using systemic steroids, 4 (3.5%) were using salazopyrin, 2 (1.7%) were using cyclophosphamide (Table 1). The patients had the chronic disease for an average of 6.5 years and had been using anti-TNF drugs for an average of 4 years. All the cases declared that they had BCG. vaccination, but six patients did not have a BCG scar. P.P.D. was performed in all of the patients, and P.P.D. response was measured as <5mm in 89 (77.4%), 5-9 mm in 11 (8.7%), 10-14 mm in 8 (7.4%), >15 mm in 7 (5.6%) cases. The IGRA test was performed on ten patients and was positive in one. Isoniazid (INH) prophylaxis was started for nine months in 17 cases with the diagnosis of latent tuberculosis (Table 1, 2). Of the 17 cases in which prophylaxis was initiated, 4 had a cough. Therefore, they were examined for active tuberculosis with Acid-Fast Stain (A.F.S.) in sputum, tuberculosis culture, tuberculosis PCR, and 2 with computed tomography. Active tuberculosis was not detected in any of the cases (Table 2). Of the 17 patients who received INH prophylaxis, nine were using etanercept, five were using infliximab, and three were using adalimumab. There was no statistically significant difference between the use of INH prophylaxis and the type and duration of the Anti-TNF agent (p:0.32) (Table 3).

Table 1. Clinical and epidemiological characteristics of the cases

	n:115 (%)		**n:115 (%)**
Age (year)	13 (2-18)		
Gender		**Chest X-Ray**	
Girl	66 (57)	Normal	113 (98.2)
Boy	49 (43)	Pathological	2 (1.8)
		TST	
JIA	76 (66.1)	0-4 mm	89 (77.3)
U. Colitis	11 (9.6)	9-10 mm	11 (9.5)
Crohn's	7 (6.1)	10-14 mm	8 (6.9)
AS	6 (5.2)	>15 mm	7 (6.1)
FMF	5 (4.3)	**Quantiferon**	
Psoriasis	4 (3.5)	Negative	9 (7.8)
Behcet	1 (0.9)	Positive	1 (0.9)
PAN	1 (0.9)		
Sarcoidosis	1 (0.9)		
Posterior Scleritis	1 (0.9)		
Etanercept	74 (64.3)	Methotrexate	66 (57)
Infliximab	17 (14.8)	Steroid	11 (9.6)
Adalimumab	17 (14.8)	Salozopyrin	4 (3.5)
Anakinra	5 (4.3)	Cylophosphamide	2 (1.7)
Canakinumab	2 (1,7)		
		ARB	
Disease Duration (month)	77 (4-204)	Negative	4 (3.5)
		Positive	0 (0)
Anti-TNF Duration (month)	45 (2-137)	Latent Tuberculosis	17 (14.8)
INH Prophylaxis	17 (14.8)	Active Tuberculosis	0 (0)

JIA: Juvenile Idiopathic Arthritis; AS: Ankylosing spondylitis; FMF: Familial Mediterranean Fever; PAN: Polyarteritis Nodosa
INH: Isoniazid; PPD: Pürified Protein Derivation; ARB: A*cid resistant* bacilli

Table 2. Characteristics of latent tuberculosis cases

	Age	Gender	Anti-TNF	Anti-TNF Duration (month)	Disease	Disease Time (year)	DMARD	BCG scar	PPD (mm)	IGST	Symptom	Chest X-ray	ARB	INH (month)
Patient-1	17	B	Etanercept	24	JIA	8	MTX	+	12	-	+	N	Negative	9
Patient-2	16	G	Adalimumab	60	JIA	11	MTX	+	16	-	-	N	-	9
Patient-3	18	G	Etanercept	48	JIA	10	MTX	+	12	-	-	N	-	9
Patient-4	16	B	Etanercept	72	JIA	14	MTX	+	20	-	+	P	Negative	9
Patient-5	17	B	Etanercept	120	JIA	12	MTX	+	14	-	-	N	-	9
Patient-6	12	G	Etanercept	54	JIA	8	MTX	+	18	Negative	-	N	-	9
Patient-7	16	G	Infliximab	12	U.Colitis	10	-	+	18	Negative	-	N	-	9
Patient-8	9	G	Etanercept	60	JIA	6	-	+	12	-	-	N	-	9
Patient-9	11	B	Adalimumab	36	JIA	6	-	+	10	-	+	N	Negative	9
Patient-10	17	B	Etanercept	60	JIA	9	MTX	+	13	-	-	N	-	9
Patient-11	17	G	Adalimumab	53	Uveitis	5	Steroit	-	19	-	-	N	-	9
Patient-12	17	B	Infliximab	46	Crohn's	4	MTX	+	11	Negative	-	N	-	9
Patient-13	17	B	Infliksimab	50	U.Colitis	4	-	-	5	-	-	N	-	9
Patient-14	4	B	Etanercept	12	JIA	2	MTX	+	10	-	+	N	Negative	9
Patient-15	16	B	Infliximab	38	Crohn's	5	MTX	+	18	-	-	N	-	9
Patient-16	17	G	Infliximab	15	Crohn's	6	Steroit	+	1	Positive	-	N	-	9
Patient-17	13	G	Etanercept	60	JIA	8	MTX	+	18	-	-	N	-	9

G: Girl, B: Boy, JIA: Juvenile Idiopathic Arthritis, AS: Ankylosing spondylitis, FMF: Familial Mediterranean Fever, PAN: Polyarteritis Nodosa, MTX: Methotrexate

Table 3. Comparison of cases who received and did not receive INH prophylaxis

	INH Prophylaxis (-) 98 (%)	**INH Prophylaxis (+) 17**	***P***
Age(year)	13 (2-20)	14 (4-18)	0.08
Gender			0.2
Girl	58 (59)	8 (47)	
Boy	40 (12)	9 (53)	
Disease			0.25
JIA	65 (66.3)	11 (64.7)	
U.Colitis	9 (9.2)	2 (11.8)	
Crohn's	4 (4.1)	3 (17.6)	
AS	6 (6.1)	-	
FMF	5 (5.1)	-	
Psoriasis	4 (4.1)	-	
Sarcoidosis	1 (1)	-	
Behcet	1 (1)	-	
PAN	1 (1)	-	
Posterior Scleritis	-	1 (5.9)	
Diease Duration(year)	6 (0.5-12)	9 (1.5-17)	0.5
Anti-TNF			0.3
Etanercept	65 (66.3)	9 (52.9)	
Infliximab	12 (12.2)	5 (29.4)	
Adalimumab	14 (14.3)	3 (17.6)	
Anakinra	5 (5.1)	-	
Canakinumab	2 (2)	-	
Anti-TNF Duration(month)	44 (2-120)	55 (12-1221	0.8
DMART			0.7
Mtx	55 (56)	11 (64.7)	
Steroid	9 (9.2)	2 (11.8)	
Salozopyrin	4 (41)	-	
Cylophosphamide	2 (2)	-	
PPD			0.001
0-4 mm	88 (89)	1 (5.8)	
5-9 mm	6 (6.1)	1 (5.8)	
10-14 mm	-	8 (47)	
>15 mm	-	7 (41.4)	
Quatiferon			0.02
Negative	6 (6.1)	3 (17.6)	
Positive	0 (0)	1 (5.9)	
ARB			0.001
Negative	-	4 (23.5)	
Positive	-	-	

JIA: Juvenile Idiopathic Arthritis, AS: Ankylosing spondylitis, FMF: Familial Mediterranean Fever PAN: Polyarteritis Nodosa INH: Isoniazid, PPD: Pürified Protein Derivativ, ARB: *Acid resistant* bacilli, MTX: Methotrexate

Discussion

With the clinical use of anti-TNF agents, significant progress has been made in treating many autoinflammatory diseases, especially rheumatologic diseases. However, it has been reported that the widespread use of anti-TNF drugs increases the risk of mycobacterial infections, especially tuberculosis (T.B.), and bacterial, viral, and fungal infections. Especially in countries with a high prevalence of tuberculosis, reactivation of latent tuberculosis infection poses an essential problem for anti-TNF therapy. The World Health Organization (WHO) report reported that the incidence of T.B. in Türkiye was 16/100.000. In patients using anti-TNF therapy, the risk of tuberculosis is 10-20 times higher than in the average population. Currently, a Guideline for Tuberculosis in Patients Using Anti-TNF Therapy was published by the Public Health Agency of the Ministry of Health, Türkiye, in 2016 [9]. Therefore, all patients scheduled for anti-TNF therapy should be screened for tuberculosis before treatment. Our study found LTBI in 17 (14.8%) of 115 cases. Similarly, in a survey conducted by Kilic et al. [13] with 144 children receiving anti-TNF in our country, they reported the rate of LTBI as 4.8% (13) (Table 1, 2). Girit et al. [14] reported the rate of LTBI before treatment as 28.1% in their study with 57 cases. There are different recommendations in different guidelines regarding the method of screening for LTBI in patients receiving anti-TNF therapy and what should be the cut-off value taken, especially for TST. While the cut-off value for TST was ≥5 mm in the American Thoracic Society guideline published in 2017, the cut-off value was recommended as ≥10 mm in the consensus report of The Tuberculosis Network European Trials Group [15, 16]. In our country, the Rheumatism Research and Education Association (RAED) recommended the TST cut-off value as 5 mm for adults and children [17]. In the Tuberculosis Guidelines for Patients Using Anti-TNF Therapy, which the Ministry of Health recently updated, Public Health Agency of Türkiye, the cut-off value is recommended as ≥10 mm for pediatric patients with BCG vaccine and ≥5 mm for those who have not been vaccinated [9]. It has been stated that concomitant rheumatic and autoimmune diseases and other concurrent immunosuppressive drugs may affect the results of TST and IGRA used to detect tuberculosis development and LTBI [9]. In our study, all cases were screened primarily with TST. The cut-off value was ≥10 mm for those vaccinated with BCG and ≥5 mm for those not vaccinated. TST value was ≥10 mm in 15 of 17 patients with LTBI diagnosis, and INH prophylaxis was started, while TST was ≥5 mm in 1 patient (patient 13), and TST was 1 mm in 1 patient (patient 16). Since the TST=5 mm case had no BCG scar and the TST=1 mm case had a positive IGRA test, which was studied simultaneously, INH prophylaxis was given to 2 patients for nine months.

Different rates have been reported in studies conducted in many other countries and centers regarding the risk of developing active tuberculosis in patients receiving anti-TNF therapy. Kilic et al. [13] reported that tuberculosis developed in 1 (0.69%) of 144 pediatric patients receiving anti-TNF therapy. Similarly, the rate of tuberculosis development was reported as 0.85% by Cagatay et al. [18] and 1.5% by Hanta et al. [19]. Contrary to these studies, Girit et al. [14] and Kurt et al. [20] reported that tuberculosis did not develop in any of the patients receiving anti-TNF. Different results have been reported in studies investigating the protection of prophylaxis for tuberculosis. Borekci et al. [12] showed no significant difference between the groups that received and did not receive INH prophylaxis regarding the development of active tuberculosis. Kaptan et al. [21] reported that active tuberculosis developed in 7 of 389 patients receiving anti-TNF therapy, and all patients received INH prophylaxis. In a multicenter study conducted by Noguera Julian et al. [22], they reported that out of 19 cases who developed tuberculosis, 15 were previously screened for LTBI, and one case was under INH prophylaxis. In our study, although 17 cases received INH prophylaxis for LTBI, none of our patients developed active tuberculosis. The absence of a case of T.B. in our study was attributed to the fact that all cases were screened appropriately for LTBI, and the administration of INH prophylaxis with patients' compliance in necessary cases reduced the risk of T.B.

Previous studies have shown that the risk of tuberculosis development differs depending on the primary disease and the type and duration of use of the Anti-TNF agent. In a

study evaluating the incidence of T.B. in 10.000 patients who received anti-TNF therapy in the U.K., it was shown that T.B. development was higher on adalimumab (144/100.000) and infliximab (136/100.000) treatments compared to etanercept (39/100.000) [23]. Active T.B. can be seen in an average of 13.6 months after etanercept treatment and 5.5 months and 18.5 months after infliximab and adalimumab treatment, respectively [23]. This is also due to the effect of infliximab on the elimination of granulysin-expressing CD45RA+ subgroups of effector memory CD8+ T cells, which are involved in the intracellular killing of M. tuberculosis [24, 25]. In another study evaluating chronic disease and TST response, the lowest response was observed in R.A. patients, while the highest response was observed in Ankylosing spondylitis (AS) patients [26]. Our study did not have any patients who developed active tuberculosis. Acid-Fast-Stain (A.F.S.), tuberculosis culture, and radiological findings were normal in the active tuberculosis screening performed in 4 patients who received INH prophylaxis for LTBI and had suspicious symptoms for tuberculosis.

The main limitations of our study are the limited number of cases, the limited information availability on patient follow-up due to the retrospective nature of the study, and the lack of Quantiferon test for most of the cases.

As a result, all patients planning to receive anti-TNF therapy should be screened for tuberculosis. Although it is not detected at the beginning of the treatment, regular tuberculosis screening should be continued during the treatment with contact history, symptoms, physical examination, chest X-ray, and TST/IGRA in light of current guidelines.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

All authors took part in the planning and design of the study. Y.K. and M.C.K. participated in data collection and statistical analysis. Y.K., M.C.K., Ö.K., and E.Ç.D. drafted the manuscript. All authors read and approved the final manuscript.