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Latent Tuberculosis Infection and Tuberculosis Development in Children Treated with Anti-TNF-α Agents

Anti-TNF-α Ajanları ile Tedavi Edilen Çocuklarda Latent Tüberküloz Enfeksiyonu ve Tüberküloz Gelişimi

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ABSTRACT

Objective: Tumor necrosis factor-α antagonists (anti-TNF-α) have improved the treatment and prognosis of patients with several rheumatologic diseases resistant to standard therapy. However, patients on anti-TNF-α agents risk various infections, especially tuberculosis (TB). We determined the incidence of latent TB infection (LTBI) and TB development and assess the follow-up protocol of patients using anti-TNF-α therapy.

Methods: Children aged under 18 years prescribed an anti-TNF-α agent were included in the study. Patients were evaluated by history, physical examination, tuberculin skin test (TST), chest X-ray, and when required, examination of sputum/early morning gastric aspirates for acid-fast bacilli and chest tomography. A TST ≥10 mm induration for patients with Bacillus Calmette-Guérin (BCG) vaccination was defined as a positive result, whereas a TST ≥5 mm for those without BCG vaccination.

Results: This study included 84 (54.2%) females and 71 (45.8%) males with a median age of 12.0 years (8.0-15.0). The most common diagnoses were oligoarticular juvenile idiopathic arthritis (JIA; n=48) and polyarticular JIA (n=38). Eight patients with positive TST results were administered isoniazid prophylaxis. New TB was determined in one patient with polyarticular JIA on infliximab and idiopathic uveitis on adalimumab. The incidence of LTBI and TB development in children on anti-TNF-α was 2.5% and 0.64%, respectively.

Conclusion: Patients on anti-TNF-α agents have a risk of TB development. TB disease is more likely to be seen in children on inflixiam and adalimumab on etanercept. It is crucial to assess these patients for TB by a pediatric pulmonologist or infectious disease at three monthly intervals.

Keywords: Anti-TNF alpha, infliximab, rheumatological disease, tuberculosis

ÖZ

Amaç: Tümör nekrozis faktörü-α antagonistleri (anti-TNF-α), standart tedaviye dirençli çeşitli romatolojik hastalıkları olan hastaların tedavisini ve prognozunu iyileştirmiştir. Bununla birlikte, anti-TNF-α ajanı kullanan hastalarda başta tüberküloz (TB) olmak üzere çeşitli enfeksiyonlar açısından risk vardır. Çalışmamızda, latent TB enfeksiyonu (LTBI) ve TB gelişimi insidansını belirlemeyi ve anti-TNF-α tedavisi kullanan hastaların takip protokolünü değerlendirmeyi amaçladık.

Yöntem: Anti-TNF-α ajanı reçete edilen ve 18 yaş altı çocuklar çalışmaya dahil edildi. Hastalar öykü, fizik muayene, tüberkülin deri testi (TST), akciğer grafisi ve gerektiğinde aside dirençli basil açısından balgam/sabah mide aspiratının incelenmesi ve akciğer tomografisi ile değerlendirildi. Bacillus Calmette-Guérin (BCG) aşısı olan hastalarda TST ≥10 mm endurasyon pozitif sonuç olarak tanımlanırken, BCG aşısı olmayanlarda TST ≥5 mm endurasyon olarak tanımlandı.

Bulgular: Bu çalışmaya ortanca yaşı 12,0 yıl (8,0-15,0) olan, 84 (%54,2) kadın ve 71 (%45,8) erkek dahil edildi. En sık tanılar oligoartiküler juvenil idiyopatik artrit (JİA; n=48) ve poliartiküler JİA (n=38) idi. Pozitif

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TST sonucu olan sekiz hastaya izoniazid profilaksisi uygulandı. İnfliksimab kullanan poliartiküler JİA ve adalimumab kullanan idiyopatik üveit olan bir hastada yeni TB saptandı. Anti-TNF-α alan çocuklarda LTBI ve TB gelişme insidansı sırasıyla %2,5 ve %0,64 idi.

Sonuç: Anti-TNF-α ajanı kullanan hastalarda TB gelişme riski vardır. TB hastalığı çocuklarda etanercepte göre infliksimab ve adalimumab kullananlarda görülme olasılığı daha yüksektir. Bu hastaların bir pediatrik göğüs hastalıkları veya enfeksiyon hastalığı uzmanı tarafından üç aylık aralıklarla TB açısından değerlendirilmesi çok önemlidir.

Anahtar Kelimeler: Anti-TNF-α, infliksimab, romatolojik hastalık, tüberküloz

INTRODUCTION

Anti-tumor necrosis factor-α (anti-TNF-α) agents have been approved for the treatment of several systemic rheumatological diseases and have improved the prognosis of patients resistant to standard therapy.[1,2] On the other hand, physiologically, TNF-α participates in different stages of defense against bacterial, viral, and mycobacterial microorganisms, especially requiring granuloma formations.[3] Therefore, anti-TNF-α agents have increased susceptibility to various infections, such as sepsis, cellulitis, bacterial pneumonia, tuberculosis (TB), and herpes zoster.[4]

The estimated deaths related to TB and active TB cases were 1.5 million and 10 million people worldwide in 2020, respectively.[5] Latent TB infection (LTBI) occurs due to exposure to *Mycobacterium tuberculosis* and progresses to active TB at a rate of 5-10%.[6] LTBI is considered when a positive TB skin test (TST) or interferon-gamma release test (IGRA) is present without any clinical, radiological, or microbiological evidence of active TB. TST is frequently used for detection of LTBI. However, immunosuppressive therapies, vaccination for TB, and the disease itself can affect the result of TST.[7] Although several guidelines suggest taking history, close contact with an individual with TB disease, chest X-ray, and TST for LTBI screening,[8,9] using TST and, if necessary, performing advanced research is recommended in Turkey.[10] Earlier studies have shown that patients treated with anti-TNF drugs have a 10-fold increased risk of LTBI reactivation.[6,11] In addition, studies from Turkey that compared patients treated with anti-TNF drugs to the general population have revealed that TB rates were between 11 and 40 times higher among those receiving anti-TNF drugs.[12-14] It was shown that isoniazid (INH) prophylaxis for LTBI notably reduced the risk of TB development in patients treated with anti-TNF-α agents. Therefore, LTBI screening and INH prophylaxis have been recommended before initiating anti-TNF-α agents.[12-15] Considering the increased risk, we aimed to establish the incidence of LTBI and TB development and assess the follow-up protocol of patients who underwent biological therapy.

METHODS

This retrospective study was conducted in a single center between July 2020 and July 2022. Children under 18 years of age prescribed an anti-TNF-α agent were included in the study. Patients without regular follow-ups were excluded. The Gazi Yaşargil Training and Research Hospital Ethics Committee approved this study (date: 21.04.2022, approval number: 75).

The following data including age, gender, follow-up time, primary illness, duration of primary disease, type of anti-TNF-α agents and other immunosuppressive drugs, duration of anti-TNF-α treatment, the presence of a Bacillus Calmette-Guérin (BCG) scar, contact with an individual with possible TB disease, TST size, chest X-ray/tomography, microbiological culture [sputum or gastric aspirate for acid-fast bacilli (AFB)], prophylaxis administration, and the presence of TB development were collected and evaluated. Before anti-TNF treatment, patients were reviewed by the history, physical examination, TST, and chest X-ray. Sputum or gastric aspirate for AFB and chest tomography were performed if required. During follow-up, patients were checked by history and physical examination at 3-month periods and chest X-ray at 6-month periods. When a positive TST was detected, INH prophylaxis (10 mg/kg/d, maximum 300 mg/d) was performed for nine months. During INH prophylaxis, anti-TNF-α therapy was stopped for one month. TST was administered with the Mantoux method. Five tuberculin units of purified protein derivative (0.1 mL) were injected into the forearm and interpreted after 48-72 hours. While a TST size ≥5 mm was considered a positive result in patients without BCG vaccination, a TST size ≥10 mm indicated a positive result in BCG-vaccinated patients.[10]

Statistical Analysis

Data are denoted as median and interquartile range. Categorized variables were presented as numbers and percentages. Statistical analyzes were performed using the statistical program package Statistical Package for the Social Sciences (version 22.0; IBM Corp., Armonk, NY).

RESULTS

Characteristics of Study Population

In our study, there were 84 (54.2%) females and 71 (45.8%) males with a median age of 12.0 years (8.0-15.0). The primary diseases of the patients were oligoarticular juvenile idiopathic arthritis (JIA; n=48), polyarticular JIA (n=38), chronic idiopathic uveitis (n=31), familial

Mediterranean fever (n=24), and systemic JIA (n=14). The duration of primary disease and anti-TNF-alfa treatment was 24.0 months (20.0-36.0) and 15 months (12.0-8.0), respectively. Etanercept (n=65; 41.9%) was the most used anti-TNF-α agent, followed by adalimumab (n=62; 40.0%) and infliximab (n=28; 18.1%; Table 1). Therapies used before anti-TNF-α agents included prednisolone (n=58), methotrexate (n=97), colchicine (n=18), azathioprine (n=12), and sulphasalazine (n=5; Table 1).

The Evaluation of Tuberculosis

Of 155 patients, 11 did not have a BCG scar (Table 1). These patients did not have a positive TST result or clinical and radiological evidence supporting active TB during the follow-up period. Contact with an individual with possible TB disease was identified in five (3.2%) patients with BCG scars (Table 1). However, after detailed interrogation of their anamnesis, we revealed no close exposure to active TB in these five patients. TST and chest X-ray were performed on these patients. Because of the negative results, INH prophylaxis was not applied. A positive TST result was revealed in eight (5.2%) patients with BCG scars. Active TB was reviewed by chest tomography and sputum/gastric aspirate for AFB. After TB disease was excluded, INH prophylaxis was administered (LTBI incidence: 2.5%; Table 2). The anti-TNF-α agent was not prescribed to these individuals for one month. Active TB did not occur in any patient after nine months. Furthermore, the clinical signs associated with primary disease also improved with anti-TNF-α treatment.

Although the chest CTs of two patients were normal, new pulmonary TB disease was diagnosed in those by ARB and TB culture positivity in gastric aspirates (TB incidence: 0.64%). Anti-TB treatment consisting of INH, rifampicin, pyrazinamide, ethambutol (2 mo), and INH + rifampicin (4 mo) was started in one patient with polyarticular JIA and chronic idiopathic uveitis (1.3%; Table 2). Patients were reviewed for the efficacy of the treatment by microbiologic culture at the end of the first month; no organism was detected. After treatment, TB symptoms were not evident in these patients. Any adverse event was not determined during TB prophylaxis or treatment.

DISCUSSION

This study showed that the incidence of LTBI and TB development in patients who underwent biological therapy was 2.5% and 0.64%, respectively. In Turkey, the rate of TB disease in children is 4.8/100000.[16] While active TB generally emerges as a reactivation of latent infection in adults, developing a primary infection in children during anti-TNF-α therapy is more common.[17] A study including 4,102 patients conducted in Spain with a similar incidence of TB (25/100,000) to Turkey reported that the rate of TB development was 0.83%.[18] Cagatay et al.[19] showed the rate of TB development to be 0.85% in patients treated with anti-TNF-α agents. In another study in which TST positivity was accepted above 10 mm, the authors found that it was 0.69%.[20] Similarly, a recently published study of 599 children on anti-TNF-α therapy determined the rate ofto bective TB be 0.69%.[21] Our results agreed with these studies from Turkey. Surprisingly, the rate of INH prophylaxis for LTBI was lower in this study (2.5%) than in other studies (8.0-16.1%). An explanation for this difference may be associated with the follow-up duration, ranging from 3 to 5 years in these studies. As a result, a

Table 1. Demographic and clinical features of the patients

Age, year	12.0 (8.0-15.0)
Male/female ratio	0.85
Primary diseases, n (%) Oligoarticular JIA Polyarticular JIA Systemic JIA Chronic idiopathic uveitis FMF	 48 (31.0) 38 (24.5) 14 (9.0) 31 (20.0) 24 (15.5)
Duration of primary diseases, month	24.0 (20.0-36.0)
Anti-TNF-α agents used, n (%) Etanercept Adalimumab Infliximab	 65 (41.9) 62 (40.0) 28 (18.1)
Duration of anti-TNF-α treatment, month	15.0 (12.0-18.0)
The presence of BCG scar, n (%)	144 (92.9)
Tuberculosis contact, n (%)	5 (3.2)

Data are given as median and interquartile range.
JIA: Juvenile idiopathic arthritis, FMF: Familial Mediterranean fever, TNF: Tumor necrosis factor, BCG: Bacillus Calmette-Guérin

Table 2. Clinical features of the patients administered INH prophylaxis and TB therapy during anti-TNF-α treatment

Patient	Age (y)	Sex	Primary disease	The time of diagnosis (y)	TNF-α therapy	The duration of TNFα therapy (mo)	TB contact	BCG scar	TST size (mm)	Chest X-ray	Previous INH prophylaxis	Gastric aspirates AFB/ Culture	Chest CT	Diagnosis	Treatment
1	10	M	FMF	2.0	Inf	18	-	+	17	N	-	-	-	LTBI	P
2	17	F	P JIA	7.3	Ada	18	-	+	15	N	-	-	-	LTBI	P
3	15	F	P JIA	6.2	Ada	22	-	+	15	N	-	-	-	LTBI	P
4	17	F	P JIA	3.5	Ada	24	-	+	13	N	-	-	-	LTBI	P
5	16	M	P JIA	2.0	Eta	16	-	+	12	N	-	-	-	LTBI	P
6	5	M	S JIA	1.5	Eta	9	-	+	11	N	-	-	-	LTBI	P
7	12	F	P JIA	2.5	Eta	12	-	+	15	N	-	-	-	LTBI	P
8	3	F	O JIA	1.6	Eta	18	-	+	13	N	-	-	-	LTBI	P
9	16	M	P JIA	3.2	Inf	10	-	+	16	N	-	+	N	TB	Anti-TB
10	8	F	Uveitis	2.0	Ada	18	-	+	12	N	-	+	N	TB	Anti-TB

TNF: Tumor necrosis factor, Y: Year, Mo: Month, TB: Tuberculosis, LTBI: Latent tuberculosis infection, BCG: Bacillus Calmette-Guérin, TST: Tuberculin skin test, INH: Isoniazid, AFB: Acid-fast bacilli, CT: Computerized tomography, M: Male, F: Female, FMF: Familial Mediterranean fever, P JIA: Polyarticular juvenile idiopathic arthritis, S JIA: Systemic juvenile idiopathic arthritis, O JIA: Oligoarticular juvenile idiopathic arthritis, Inf: Infliximab, Ada: Adalimumab, Eta: Etanercept, N: Normal, P: Prophylaxis, Anti-TB: Anti-tuberculosis

longer follow-up time may result in the determination of a higher rate of LTBI.

As a first-line approach in the present study, a detailed history, physical examination, TST, and chest X-ray were used to evaluate patients before anti-TNF-α therapy regarding LTBI and active TB. When suspected of TB reactivation, chest tomography and microbiological culture were performed. We followed up with all patients at three-month intervals. Considering the assessment protocol for patients on anti-TNF-α therapy, it has been shown by effective results to monitor patients for LTBI closely and administer appropriate treatment.[20] INH for nine months or rifampicin for four months is recommended for LTBI prophylaxis. In addition, starting anti-TNF-α agents one month after prophylaxis is suggested when patients have a clinically stable rheumatologic disease. On the contrary, prophylaxis and anti-TNF-α agent should be started simultaneously in patients with clinically active rheumatologic disease and followed up closely.[10]

Although TST and IGRA are frequently used for LTBI screening, there is no consensus on which method is more valuable. According to the Canadian Tuberculosis Committee Guidelines, an IGRA may be applied after the initial TST is a negative result in an immunocompromised patient within the presence of concern about LTBI.[22] The American Thoracic Society and Center for Disease Control recommend using TST and IGRA if the initial test is a negative result and the risks of disease progression, probably infected, and a poor outcome are existed.[23] On the other hand, the Royal College of Physicians and the European Tuberculosis Network European Trials Group Consensus Statement suggest using TST and IGRA for all individuals treated with an anti-TNF-α agent.[15] The sensitivity and reliability of TST are affected by some conditions, such as immunosuppression, the disease itself, or corticosteroids.[21] However, in vitro studies suggested that IGRA was influenced by various immunosuppressive drugs, including infliximab, calcineurin inhibitors, and corticosteroids.[24,25] In this study, we reviewed patients using TST and chest X-ray at the beginning of the anti-TNF-α therapy. We could not use the IGRA test in this study because it was unavailable in our center. Therefore, we note that it is likely possible to have more false-negative results by performing only TST compared with apply a TST and an IGRA test simultaneously.

Most studies have suggested that the rate of TB reactivation was higher in patients treated with adalimumab and infliximab than in those treated with etanercept.[21,26,27] Dixon et al.[28] conducted a study including approximately 14000 patients receiving anti-TNF-α therapy. The authors reported a higher rate of TB in patients receiving

adalimumab or infliximab (144 and 136 events per 100,000 patients person-years) than in those receiving etanercept (39 events per 100,000 patients person-year). Similarly, two patients were diagnosed with new TB in this study. While infliximab was prescribed to one of them, the other received adalimumab. There are several possible explanations for these differences among anti-TNF-α agents. Infliximab shows more affinity to TNF receptor 1 which plays a crucial role in the defense against TB, whereas etanercept to TNF receptor 2.[28] Another explanation might be that infliximab and adalimumab reduce interferon production by about 65-70%.[29] Furthermore, it has been shown that infliximab and adalimumab decreased the rate of TB-responsive CD4 cells, whereas etanercept did not.[29] Therefore, TB reactivation can be more common in patients receiving adalimumab and infliximab than in those treated with etanercept.

Study Limitations

There were several limitations. First, this study was a retrospective study based on medical records. Therefore, a standardized form was used to collect the data, and only necessary information was handled. Additionally, the same clinician collected data. Second, screening patients on immunosuppressive therapy with TST and IGRA simultaneously can achieve greater sensitivity. In this study, IGRA could not be applied to our patients, so we might have a higher rate of false negative results. Lastly, most of our patients were treated with other immunosuppressive drugs before LTBI screening, and it is possible that TST results may be affected.

CONCLUSION

Children treated with anti-TNF-α agents have a risk of active TB development. It is essential to assess patients for LTBI and TB by detailed history, physical examination, TST, and chest X-ray. Besides, effectively treating LTBI can decrease the rate of active TB. Our data showed that LTBI and active TB rates were 2.5% and 0.64%. TB disease is more likely to be seen in those on inflixiam and adalimumab than in those on etanercept. Close follow-up and high suspicion may prevent the development of active TB in patients treated with anti-TNF-α agents.

Ethics

Ethics Committee Approval: The Gazi Yaşargil Training and Research Hospital Ethics Committee approved this study (date: 21.04.2022, approval number: 75).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.E., V.Ş., Design: A.E., V.Ş., Data Collection or Processing: A.E., Analysis or Interpretation: A.E., V.Ş., Literature Search: A.E., V.Ş., Writing: A.E., V.Ş.

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