Ann Med Res 2020;27(6):1751-5

Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.12.899

Original Article

Monitorization of tuberculosis screening tests during anti-TNF-α treatment in children with rheumatic diseases

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Abstract

Aim: We aimed to investigate the incidence of latent tuberculosis infection (LTBI) and seroconversion rate of LTBI screening tests under anti-TNF-α treatment, in our pediatric patients with chronic rheumatic diseases.

Material and Methods: The data of 47 patients received anti-TNF-α treatment for different chronic rheumatic diseases between May-2015 and May-2018, were reviewed retrospectively. Demographics and clinical findings of the patients, as well as the treatments and their durations, were collected. The tuberculin skin test (TST) and Quantiferon-TB-Gold in-tube (QFT) test results at initiation and one year after the anti-TNF-α treatment were compared.

Results: The study group included 38 (80.8%) patients with juvenile idiopathic arthritis, six (12.7%) with idiopathic uveitis, two (4.2%) with Behçet's disease related uveitis and one (2.1%) with juvenile dermatomyositis. For a period at least one year, 33 (70.2%) patients received etanercept, 12 (25.5%) received infliximab and two (4.2%) received adalimumab treatment. Before anti-TNF-α treatment, 31.9% of the patients were diagnosed with LTBI. After one year of treatment, it was found to be increased to 44.6%. During treatment, the seroconversion rate of the screening tests for LTBI was determined to be 12.7% (6/47).

Conclusion: The seroconversion rate of screening tests for LTBI was found high in pediatric patients receiving anti-TNF-α treatment. Although the consistency between TST and QFT tests was found weak in our study, the fact that these tests should be used and evaluated together in the follow-up in the light of current guidelines in terms of LTBI and active tuberculosis development, remains still up to date. Further research is need in order for more enlightening data on the risk of LTBI and active tuberculosis in patients under anti-TNF-α treatment.

Keywords: Anti-TNF-α therapy; latent tuberculosis infection; pediatric rheumatology; tuberculin skin test; quantiferon

INTRODUCTION

Tuberculosis is one of the major infection with increased risk of occurrence in patients treated with biological agents, particularly anti-TNF-α treatments (1,2). Active tuberculosis infection may develop within the first 2 years in 5% of individuals who have encountered with *Mycobacterium tuberculosis*. In the remaining individuals, the microorganism is carried on for many years, of which is called latent tuberculosis infection (LTBI) (3). 80% of tuberculosis infections develop with the conversion of LTBI present in individuals to active tuberculosis infection over time (4). In the presence of immunosuppressive conditions such as biological therapies, other immunosuppressive treatments, immunosuppressive diseases, advanced age and HIV-infection, there is an increased risk of LTBI reactivation and conversion of it to active tuberculosis infection. In this context, the patients treated with biological therapies, especially anti-TNF-α treatments, must be screened for the presence of active tuberculosis infection and LTBI.

In the national and international guidelines, patients treated with anti-TNF-α treatment are categorized in immunosuppressed patients group and it is recommended that these patients to be evaluated with contact and family history, chest X-ray, and tuberculin skin test (TST) or interferon gamma release assay (IGRA) (5). In pediatric patients receiving anti-TNF-α treatment, there is not enough data about the seroconversion rate of these serological tests in the follow-up. In various studies in which the adult patients under the biological therapies with chronic inflammatory diseases are included, it was demonstrated that the seroconversion rates in the screening tests for LTBI was varied between 0.5% and 37% (6-8). In our study, we aimed to investigate the incidence of LTBI and active tuberculosis infection, and to demonstrate the conversion rate of TST and IGRA results before and during the treatment in our pediatric patients under anti-TNF-α treatment with different chronic rheumatic diseases

Received: 29.12.2019 **Accepted:** 11.02.2020 **Available online:** 19.06.2020
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MATERIAL and METHODS

This is a retrospective study involving patients between May 1, 2015 and May 1, 2018. It was carried out by the Karadeniz Technical University, Faculty of Medicine, Department of Pediatric Rheumatology. The protocol of the study was approved by the local Ethics Committee of the Karadeniz Technical University, Faculty of Medicine. The study was conducted in accordance with the Declaration of Helsinki. The data of the patients diagnosed with chronic rheumatic diseases and received anti-TNF-α treatment due to resistance of the other disease-modifying anti rheumatic drugs (DMARDs) over the three-year period were reviewed. Among these patients, those who received anti-TNF-α treatment for at least 12 months were included in to the study. The patients who received different biological therapies or immunosuppressive treatments concomitantly or earlier, who have a history of treatment for tuberculosis infection or prophylaxis for LTBI, and who have findings in chest X-rays suggesting previous or new tuberculosis infection, were excluded. For the 47 patients in total who were treated with anti-TNF alpha treatment due to different chronic rheumatic diseases, TST, IGRA and P-A chest X-ray results which were assessed before and one year after treatment, were reviewed. The patients were defined as seroconverters whom had negative LTBI screening test in pre-treatment and at least one of these tests were found positive in the 12th month of treatment. In these patients, the development of active tuberculosis infection or LTBI, and correlation and seroconversion status of screening tests for LTBI were evaluated.

The tuberculin skin test was performed by subcutaneous administration of purified protein derivatives (PPD) obtained from *Mycobacterium tuberculosis*, to the interior surface of the right or left forearm of each patient in a dose of five units of tuberculin (0.1 ml), and measuring the largest diameter of the induration at the administration site at hour 72 by the same observer, and recorded in millimeters. The cases with a negative result for TST were re-assessed two weeks later using TST, and the results obtained were recorded. "Quantiferon-TB Gold in-tube (QFT)" test which, measures the level of interferon gamma release, was assessed from peripheral blood samples collected from patients before TST was performed. Appropriate with the national and international treatment guidelines prepared for tuberculosis screening in patients receiving anti-TNF-α treatment, the patients with TST and/or QFT positivity were evaluated as having LTBI and treated with isoniazid prophylaxis for nine months (9,10). Since our patients were receiving methotrexate or salazopyrin as DMARDs prior to biological therapy, and were under anti-TNF-α treatment one year later, our patients were considered as the immunosuppressed group and the cases with a TST ≥5 mm were assessed as positive for LTBI (9-11). In the patients who received isoniazid prophylaxis, anti-TNF-α treatment was initiated at least one month after the onset of prophylaxis. Data of our patients, such as demographics, sub-type and duration of the disease, comorbid diseases, and DMARDs or biological therapies that have been received by the patients and the duration of these treatments, were also collected from patient files.

Statistical package for the social sciences (SPSS) (version 23.0, SPSS-Inc., Chicago, IL, USA) was used for statistical analysis. Categorical data were presented as numbers (n) and percentage (%) while the continuous variables are presented as mean ± standard deviation (SD). Pearson chi-square test was used to assess the categorical variables and the distribution between the two groups for continuous variables was compared with Student's T test. A p-value of <0.05 was considered as statistically significant.

RESULTS

Our study group included a total of 47 patients, 23 (48.9%) male and 24 (51.1%) female. The mean diagnosis age of our patients was 103.7±59.7 months (female: 89.4±52.1, male: 118.7±64.5). The study group included 38 (80.8%) patients with juvenile idiopathic arthritis (JIA), six (12.7%) with idiopathic uveitis, two (4.2%) with Behçet's disease (BD) related uveitis and one (2.1%) with juvenile dermatomyositis, respectively (Table 1). Of the patients diagnosed with JIA; four (10.5%) had extended oligoarticular JIA, 16 (42.1%) had persistent oligoarticular JIA, nine (23.6%) had RF(-) polyarticular JIA, one had RF(+) polyarticular JIA, six had enthesitis-related arthritis, and two had psoriatic arthritis. Among the patients with JIA, it was determined that two patients had familial Mediterranean fever (FMF), two had Henoch-Schönlein purpura (HSP) and four had uveitis, as comorbid conditions. The anti-TNF-α treatments used by the patients are as follows: etanercept in 33 (70.2%) patients, infliximab in 12 (25.5%) and adalimumab in two (4.2%). The study group was consist of patients that received anti-TNF-α treatment for a minimum of 12 months. Anti-TNF-α therapy was discontinued in 10 patients due to unresponsiveness to the treatment and in four patients due to achieving remission. For the remaining 33 patients, anti-TNF-α treatment was still ongoing until the end of the study. The average treatment duration was determined as 22.7±8.9 months. As DMARDs, 33 patients were receiving methotrexate, six were sulfasalazine and one was azathioprine (Table 1).

All patients in the study group are BCG-vaccinated and had one BCG scar. In the both, before and one year after periods with the anti-TNF-α therapy, all of the 47 patients were evaluated with TST while QFT was performed in 35 patients. In the pre-treatment period, 13 (27.6%) patients with TST positivity, one with QFT positivity and one with TST and QFT co-positivity were evaluated as having LTBI. The rate of LTBI was 31.9% (15/47) in the period prior to anti-TNF-α therapy. Isoniazid prophylaxis was given to patients with normal chest X-rays and no signs suggesting active tuberculosis infection, for nine months.

Table 1. Demographic and general characteristics of patient groups

Characteristics	All patients (n=47)	Seroconverters[#] (n=6)	Non-Converters (n=41)	p value
Gender % (F/M)	51.1/48.9	50/50	51.2/48.7	0.66
Age at diagnosis*	103.7±59.7	104.0±62.9	103.7±60.1	0.51
Disease duration*	45.2±21.4	43.4±13.7	45.4±22.3	0.54
Biologic therapy duration*	22.7±8.9	24.6±6.6	22.4±9.1	0.11
Disease (n)				0.74
Juvenile idiopathic arthritis	38	5	35	
Idiopathic uveitis	6	1	3	
Behçet's Disease	2	0	2	
Juvenile Dermatomyositis	1	0	1	
DMARD therapies (n)				0.80
Methotrexate	33	4	29	
Sulfasalazine	6	1	5	
Azathioprine	1	0	1	
Anti-TNF-α therapies (%)				0.82
Etanersept	33	5	28	
İnfliksimab	12	1	11	
Adalimumab	2	0	2	

*Periods are presented as mean-standard deviation in months
[#] The patients were defined as seroconverters whom had negative LTBI screening test in pre-treatment and at least one of these tests were found positive in the 12th month of treatment

In the results of the LTBI screening tests repeated on one year later, 14 of 47 patients had only TST positivity, one had QFT positivity, and six had TST and QFT co-positivity. The incidence of LTBI was found 44.6% (21/47) in the 12th month of treatment. After one year of treatment, it was determined that the screening tests were converted to positive for TST in five patients, QFT in four patients and both TST and QFT in one patient. TST and QFT seroconversion were seen in six (12.7%) and five (10.6%) patients after one year of treatment, respectively. Four of the five patients in whom QFT converted to positive after treatment, were in the LTBI group due to TST-positivity in the pre-treatment period. Compared to pre-treatment period, the overall seroconversion rate for LTBI was 12.7% (6/47) (Table 2). Also, isoniazid prophylaxis was started and anti-TNF-α treatment was break for one month to the patients with seroconversion in LTBI tests. In both pre- and post-treatment periods, it was demonstrated that the QFT tests were negative in the majority of patients with TST positivity, as well as TST and QFT positivity were not consistent with each other. There was no significant difference between demographic and general characteristics of patients with and without seroconversion (Table 1).

Table 2. Seroconversion rates of LTBI screening tests before and after anti-TNF-α treatment

Before treatment	Patients (n)	At the 12 month of treatment	Patients (n)
TST and QFT negative	32	TST and QFT negative	26
TST positivity	13	TST positivity	14*
QFT positivity	1	QFT positivity	1
TST and QFT co-positivity	1	TST and QFT co-positivity	6[#]

TST: The Tuberculin Skin Test, QFT: "Quantiferon-TB Gold in-tube" Test, * TST positivity was observed in six new patients,
[#] Five of the patients with QFT positivity were the TST positive patients before treatment

DISCUSSION

It is a known fact that anti-TNF-α treatments pose a risk for development of tuberculosis (12). There is not enough data about the incidence of LTBI screening tests and the presence of active tuberculosis in children with rheumatic diseases who are receiving biological treatments, and about its seroconversion after treatment. Our study is one of the first studies investigating the frequency of LTBI before and after treatment in pediatric patients receiving anti-TNF-α treatment in our country. In this study, we determined the prevalence of LTBI and the frequency of seroconversion in screening tests for LTBI after anti-TNF-α treatment in patients with juvenile chronic rheumatic disease.

In pediatric patients received anti-TNF-α treatment, there are a limited number of studies evaluating conversions and correlations of screening tests for LTBI. In different studies conducted in various countries including adult patients, the pre-treatment incidence of LTBI was varied between 9.4%-14.6% (13-15). In a study conducted by Ramos et al., in which 115 patients with different diagnoses were evaluated prior to biological treatment, the incidence of LTBI was found to be as high as 45.2%. Similar studies have shown that seroconversion rates with anti-TNF-α treatment in LTBI screening tests range from 9.4% to 19.2% (13, 16, 17). In a recent meta-analysis, 88 different studies involving more than 200,000 individuals from 36 countries have been examined in terms of LTBI prevalence. It was demonstrated that IGRA positivity was 24.8% and TST positivity (>10mm) was 21.2%, and one quarter of the world's population was considered to be infected with one of LTBI (18). Seroconversion rates in patients receiving anti-TNF-α treatment have also been reported to vary depending on the test. These rates were reported to be between 0% to 12% for the IGRA assays, while reported to be between 25% to 37% for TST. Differences in the seroconversion of LTBI screening tests during the treatment have been reported among the populations, and rates for tuberculosis have been demonstrated to be in the range of 0%-13.6% in low-risk countries and in the range of 25%-37% in high-risk populations including our country (6-8). In our study, the seroconversion rate for TST was 12.7% while it was 10.6% for QFT. The relatively high rate of QFT seroconversion was thought to be due to the fact that the majority of these patients consisted of patients who were evaluated as LTBI with TST positivity before treatment. In a recent research conducted in our country, 57 patients being followed-up with a diagnosis of juvenile-onset autoimmune disease who received anti-TNF-α treatment had LTBI rates of 31.5% and 33.3% before and at the sixth month of treatment, respectively. During the treatment, seroconversion rate was as low as 1.8%. In the same study, it was found that TST has poor correlation with IGRA, and reported that the rates of TST-positivity were higher (19). We found similar data with the results of the study of Girit et al., and the incidence of LTBI was determined as 31.9% in our patients in the pre-treatment period. In contrast to Giritli et al., after the anti-TNF-α treatment, the incidence of LTBI was 44.6% and the seroconversion rate for LTBI screening tests was 12.7% in our study group, and these rates were determined to be higher. Considering the fact that our society is a high-risk population in terms of encountering "*Mycobacterium tuberculosis*" and of tuberculosis infection, the pre-treatment incidence of LTBI in our patient group was not considered as very high. The frequency of seroconversion in our study is similar to the studies in adult patients receiving biological treatment and the rates in countries with low prevalence of tuberculosis (20). The frequency of LTBI before and after anti-TNF-α treatment in our patients was determined as 31.9% and 44.6%, which are above these rates. The reason for the higher frequency of LTBI in our patients was considered to be the conventional DMARDs and biological therapies they received in this period, and a positive TST cut-off value (> 5mm) on this basis.

In various studies in the literature, anti-TNF-α treatments have been reported to pose a risk for tuberculosis and active tuberculosis may develop in patients under treatment (21,22). The emergence of active tuberculosis frequency in patients with LTBI with rheumatic diseases receiving anti-TNF-α treatment was determined to be varied between 0.2%-4% (20). Therefore, it was recommended by the American College of Rheumatology that these patients should be evaluated annually by TST and QFT tests (5). Likewise, in our country, annual screening for LTBI is recommended in the guideline for tuberculosis, published by the Ministry of Health, for patients receiving anti-TNF-α treatment (10). In our patients monitored for LTBI in line with the recommendations, no active tuberculosis development was observed during treatment.

The limitations of our study can be listed as the low number of patients, the inability to perform screening with QFT in all patients and the retrospective nature of the study. Further prospective studies including more patients, reporting the results of LTBI screening tests evaluated during the first year of follow-up and reviewing risk factors, will be useful in revealing more enlightening data to elucidate the risk of LTBI and active tuberculosis in patients under anti-TNF-α treatment.

CONCLUSION

In conclusion, in our pediatric patients with rheumatic diseases receiving anti-TNF-α treatment, LTBI was observed in nearly half of the patients while no development of active tuberculosis was observed. In Turkey, seroconversion rates for LTBI screening test in pediatric patients receiving anti-TNF-α treatment are similar to the results in low-risk populations. Although the consistency between TST and QFT tests is weak, the fact that these tests should be used and evaluated together during monitorization in the light of current guidelines in terms of LTBI and active tuberculosis development remains still up to date. In these patient groups, further research is need in order for more informative data on the risk of LTBI and active tuberculosis to be revealed.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Ethics Committee of the Karadeniz Technical University, Faculty of Medicine (2018/155-16.07.2018)

REFERENCES

1. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38:1261-5.
2. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum 2005;52:1766-72.
3. World Health Organization. Global tubercolosis report 2019. https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1.
4. Centers for Disease Control and Prevention. Burden of TB in the United States. https://www.cdc.gov/features/burden-tb-us/index.html.
5. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625-39.
6. Hatzara C, Hadziyannis E, Kandili A, et al. Frequent conversion of tuberculosis screening tests during anti-tumour necrosis factor therapy in patients with rheumatic diseases. Ann Rheum Dis 2015;74:1848-53.
7. Bermejo F, Algaba A, Chaparro M, et al. How frequently do tuberculosis screening tests convert in inflammatory bowel disease patients on anti-tumor necrosis factor-α? A pilot study. Dig Liver Dis 2013;45:733-7.
8. Sadovici-Bobeica V, Salaru V, Mazur L, et al. Conversion of tuberculosis screening tests during biological therapy in patients with rheumatic diseases: what's beyond screening values? Eur Respir J 2018;52:5280
9. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis 2017;64:1-33.
10. Tüberküloz Tanı ve Tedavi Rehberi, Ankara: TC Sağlık Bakanlığı, Türkiye Halk Sağlığı Kurumu 2019.
11. Kalfa M, Aksu K. Treatment with tumor necrosis factor-alpha antagonists and infections. RAED J 2011;3:49-56.
12. Dixon WG, Hyrich KL, Watson KD. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69:522-8.
13. Cuomo G, D'Abrosca V, Iacono D, Pantano I. The conversion rate of tuberculosis screening tests during biological therapies in patients with rheumatoid arthritis. Clin Rheumatol 2017;36:457-61.
14. Nobre CA, Callado MR, Lima JR, et al. Tuberculosis infection in rheumatic patients with infliximab therapy: experience with 157 patients. Rheumatol Int 2012;3:2769-75.
15. Marques CDL, Duarte ALBP, Lorena VMB, et al. Attenuated response to PPD in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis. Rev Bras Reumatol 2009;49:121-31.
16. Cerda OL, de Los Angeles Correa M, Granel A, et al. Tuberculin test conversion in patients with chronic inflammatory arthritis receiving biological therapy. Eur J Rheumatol 2019;6:19-22.
17. Ramos S, Nogueira A, Dias A, et al. Tuberculosis screening in patients receiving biological therapy. Acta Reumatol Port 2015;40:234-40.
18. Cohen A, Mathiasen VD, Schön T, et al. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. Eur Respir J 2019;54.
19. Girit S, Ayzıt Atabek A, Senol E, et al. Screening for latent tuberculosis in children with immune-mediated inflammatory diseases treated with anti-tumor necrosis factor therapy: Comparison of tuberculin skin and t-spot tuberculosis tests. Arch Rheumatol 2020;35:1-9.
20. Garcovich S, Ruggeri A, D'Agostino M, et al. Clinical applicability of Quantiferon-TB-Gold testing in psoriasis patients during long-term anti-TNF-alpha treatment: a prospective, observational study. J Eur Acad Dermatol Venereol 2012;26:1572-6.
21. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al; START Study Group. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 2006;54:1075-86.
22. Chen DY, Shen GH, Chen YM, et al. Biphasic emergence of active tuberculosis in rheumatoid arthritis patients receiving TNFα inhibitors: the utility of IFNγ assay. Ann Rheum Dis 2012;71:231-7.