Evaluation of Tuberculosis in Children Using Biological Agent Therapy

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Abstract

Introduction: Treatment with biological agents, which are classified as monoclonal antibodies, cytokines and fusion proteins, increases patient risk for developing tuberculosis (TB) and non-tuberculous mycobacterial infections. In this study, we aimed to investigate the risk of tuberculosis development in pediatric patients using anti-TNF drugs.

Method: One hundred and fifteen pediatric cases who were followed up in Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics between January 2011 and December 2021 and received anti-TNF and biological agent treatment 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 mean age of the cases was 13 (2-18) years. Of the cases, 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%). 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 using in 2 (%1.7) cases. PPD was performed in all of the cases and PPD 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 9 months in 17 cases with the diagnosis of latent tuberculosis. Active tuberculosis was not detected in any of the cases.

Conclusion: All patients who are planned to receive anti-TNF therapy should be definitely screened for tüberculosis. 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 the light of current guidelines

Key Points

-We investigated the risk of tuberculosis in pediatric patients receiving anti-TNF therapy.

-The most common disease was Juvenile Rheumatoid Arthritis, while the most commonly used biological agent was etanecept.

-While Isoniazid (INH) prophylaxis was given to 17 cases, we did not have any active tuberculosis patients under prophylaxis.

Introduction

Tumor Necrosis Factor-alpha (TNF-alpha) is a proinflammatory cytokine that plays an important 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 important role in the pathogenesis of inflammation in many diseases. Therefore, in recent years, TNF-alpha inhibitors used in the treatment of autoimmune and inflammatory diseases such as Juvenile Idiopathic Arthritis (JIA), Rheumatoid Arthritis (RA), 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 (5,6,7,8). Anti-TNF agents are effective in autoimmune diseases by suppressing inflammation, but also they increase the risk of granulomatous infections such as Histoplasma capsulatum, Nocardia, especially tuberculosis, by preventing granuloma formation, chemotaxis of neutrophils and macrophages, and cytokine release (3,4).

Tuberculosis is a global public health problem, which is thought to affect 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 mostly the lungs, other organs and systems may also be affected. It has been reported that the risk of latent TB reactivation increases up to 11-40 times in patients receiving anti-TNF therapy. 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 (9,10,11). During screening, patients should be evaluated with their medical history, physical examination findings, tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA) and chest radiographs. The use of TNF-alpha inhibitors is contraindicated as soon as active TB 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.

Method

One hundred and fifteen pediatric cases who were followed up in our University Faculty of Medicine, Department of Pediatrics between January 2011 and December 2021 and received anti-TNF and biological agent treatment were 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, 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 3 months, chest X-ray every 6 months, and TST test once a year. The Mantoux method was used for TST. For this purpose, 5 units of PPD were injected intradermally into the ulnar surface of the forearm and the transverse diameter of the induration was measured 48-72 hours later. The TST result was evaluated according to

the current guideline recommendations of the time in which 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 vaccinated with BCG. In patients who did not react, the test was repeated 10 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 9 months for prophylactic treatment in cases diagnosed with LTBI.

Statistical Analysis

IBM SPSS Statistics 18 package program was used in the analysis of the data in the study. Central and prevalence measures such as number, percentage, minimum, maximum values, mean, median, and standard deviation were used in the creation of 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 cases, 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 using in 2 (%1.7) cases. In cases 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 chronic disease for an average of 6.5 years, and they had been using anti-TNF drugs for an average of 4 years. All of the cases declared that they had BCG vaccination, but 6 of the cases did not have BCG scar. PPD was performed in all of the cases and PPD 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. IGRA test was performed on 10 cases, and it was positive in one. Isoniazid (INH) prophylaxis was started for 9 months in 17 cases with the diagnosis of latent tuberculosis(Table-1). Of the 17 cases in which prophylaxis was initiated, 4 had cough therefore they were examined for active tuberculosis with Acid-Fast Stain (AFS) in sputum, tuberculosis culture, tuberculosis PCR and 2 with computed tomography. Active tuberculosis was not detected in any of the cases(Tabe-2). Of the 17 patients who received INH prophylaxis, 9 were using etanercept, 5 were using infliximab, and 3 were using adalimumab. There was no statistically significant difference between the use of INH prophylaxis and the type and duration of Anti-TNF agent((p:0.32)(Table-3).

Discussion

With the clinical use of anti-TNF agents, significant progress has been made in the treatment of many autoinflammatory diseases, especially rheumatologic diseases. It has been reported that the widespread

use of anti-TNF drugs increases the risk of mycobacterial infections, especially tuberculosis (TB), and bacterial, viral and fungal infections. Especially in countries with a high prevalence of tuberculosis, reactivation of latent tuberculosis infection poses an important problem for anti-TNF therapy. In the report of the World Health Organization (WHO), the incidence of TB in Turkey was reported to be 16/100.000, and the risk of TB development was reported to be 10-20 times higher in the use of Anti-TNF biological agents (5,10). Currently, a Guideline for Tuberculosis in Patients Using Anti-TNF Therapy was published by the Public Health Agency of the Ministry of Health, Turkey in 2016(9). According to this; all patients for whom TNF-alpha inhibitor treatment is decided are screened for LTBI with TST or IGRA before receiving Anti TNF-alpha treatment. In our study, LTBI was found in 17 (14.8%) of 115 cases. Similarly, in a study conducted by Kılıç et al. with 144 children receiving anti-TNF in our country, they reported the rate of LTBI as 4.8%(13). Girit et al. reported the rate of LTBI before treatment as 28.1% in their study with 57 cases(14).

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 was recently updated by the Ministry of Health, Public Health Agency of Turkey, 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 immunosuppressive drugs used concurrently may affect the results of TST and IGRA used for detection of tuberculosis development and LTBI(9). In our study, all cases were screened primarily with TST, and the cut-off value was ≥10 mm for those vaccinated with BCG and ≥5 mm for those who were 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 positive IGRA test, which was studied simultaneously, INH prophylaxis was given to 2 cases for 9 months.

Different rates have been reported in studies conducted in many different countries and centers in terms of the risk of developing active tuberculosis in patients receiving anti-TNF therapy. Kilic et al. reported that tuberculosis developed in 1 (0.69%) of 144 pediatric patients receiving anti-TNF therapy(13). Similarly, the rate of tuberculosis development was reported as 0.85% by Çağatay et al., and 1.5% by Hanta et al(18,19). Contrary to these studies, Girit et al. and Kurt et al. reported that tuberculosis did not develop in any of the patients receiving anti-TNF(14,20). Conflicting results have been reported in studies examining the benefit of prophylaxis for LTBI. In the study of Börekçi et al., the development of TB in cases receiving anti-TNF treatment did not differ significantly between the groups that received and did not receive INH prophylaxis (12). In the study of Kaptan et al., active tuberculosis developed in 7 of 389 cases who received anti-TNF treatment, and they reported that all cases received INH prophylaxis (21). In a

multicenter study which is conducted by Noguera-Julian et al., they reported that out of 19 cases who developed tuberculosis, 15 were previously screened for LTBI and 1 case was under INH prophylaxis(22). In our study, although 17 cases received INH prophylaxis for LTBI, none of our patients developed active tuberculosis. The absence of a case of TB 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 TB.

In previous studies, it has been shown that the risk of tuberculosis development is different depending on the primary disease and the type and duration of use of the Anti-TNF agent. In a study evaluating the incidence of TB in 10,000 patients who received anti-TNF therapy in the UK, it was shown that TB development was higher on adalimumab (144/100,000) and infliximab (136/100,000) treatments compared to etanercept (39/100,000) (23). Active TB can be seen in an average of 13.6 months after etanercept treatment is started, 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 RA patients, while the highest response was observed in Ankylosing spondylitis (AS) patients(26). In our study, we did not have any patient who developed active tuberculosis. Acid-Fast-Stain (AFS), tuberculosis culture and radiological findings were found to be 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 who are planned to receive anti-TNF therapy should be definitely 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 the light of current guidelines.

Declarations

Ethics approval and consent to participate: For this study, approval was obtained from the Eskişehir Osmangazi University Ethics Committee with the number: 05 and dated 28.08.2021.

Consent for publication: Publication approval was obtained from all authors.

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

Author contributions: All authors took part in the planning and design of the study. Y.K. and M.C.K participated in data collections 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.

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Tables

Tables 1 to 3 are available in the Supplementary Files section

Supplementary Files

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